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

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Abstract

Objectives—Fixed-dose rate gemcitabine plus docetaxel is active as second-line therapy for metastatic uterine leiomyosarcoma. We sought to determine the activity of this regimen as first-line treatment.

Methods—Eligible women with advanced uterine leiomyosarcoma were treated with gemcitabine 900 mg/m^2 over 90 minutes, days one and eight, plus docetaxel 100 mg/m^2 on day eight, with granulocyte growth factor support day nine of a 21-day cycle. Patients with prior pelvic radiation received lower doses. Patients were treated until progression or unacceptable toxicity. Response was assessed every other cycle by RECIST.

Results—Forty-two women enrolled, with 39 evaluable for response. Objective responses were observed in 15 of 42 patients (35.8% overall; complete response 4.8%, partial response 31%, 90% confidence interval 23.5 to 49.6%), with an additional 11 (26.2%) having stable disease. Nineteen of 38 (50%) received six or more cycles of study treatment. Myelosuppression was the major toxicity: neutropenia grade 3 in 5%, grade 4 in 12%; anemia grade 3 in 24%; thrombocytopenia grade 3 in 9.5%, grade 4 in 5%. One patient had a grade 3 allergic reaction, 17% had grade 3 fatigue. One possibly-related grade 4 pulmonary toxicity was observed. The median progression-free survival (PFS) was 4.4 months (range 0.4 to 37.2+ months). Among 15 women with objective response, median response duration was six months (range 2.1 to 33.4+ months). Median overall survival was 16+ months (range: .4 − 41.3 months)

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AUTHORS DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

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Précis

Gemcitabine plus docetaxel achieves high objective response rates in metastatic uterine leiomyosarcoma as first-line therapy.

Conclusion—Fixed-dose rate gemcitabine plus docetaxel achieves high objective response rates as first-line therapy in metastatic uterine leiomyosarcoma.

Keywords

gemcitabine; docetaxel; uterine leiomyosarcoma

INTRODUCTION

Background

Doxorubicin-based therapy has been the mainstay of first-line therapy for metastatic, unresectable soft tissue sarcomas, including uterine leiomyosarcomas, for decades. Single-agent doxorubicin remains standard first-line therapy in many treatment settings, with first-line response rates of approximately 25% [1,2]. The combination of doxorubicin plus ifosfamide (response rate 28−30%) has not been shown to improve outcomes among patients with soft tissue sarcoma compared with doxorubicin alone [3,4]. Other single agents with moderate activity in leiomyosarcoma include ifosfamide (response rate 17.2%), gemcitabine (bolus infusion achieved a 20% response rate among women with uterine leiomyosarcoma), ecteinascidin-743 (response rate of 8% among patients with prior treatment, and 17% as first-line therapy) and temozolomide (15.5% objective response with daily oral treatment) [5-9]. Multiple chemotherapy agents, including cisplatin, mitoxantrone, amonifide, oral etoposide, diazoquone (AZQ), intravenous etoposide, topotecan, paclitaxel, thalidomide, and trimetrexate have been tested in the first and second-line setting with negligible activity demonstrated [10-20].

Fixed-dose rate infusion of gemcitabine is a term that refers to infusing the gemcitabine at a rate that maintains the gemcitabine concentration at a level that optimizes the incorporation of the active gemcitabine metabolite, gemcitabine triphosphate, into deoxyribonucleic acid (DNA). Pre-clinical data have shown that maintaining the gemcitabine triphosphate concentration at 20 umol/liter, optimizes *in vivo* cell kill [21,22]. Pharmacokinetic analyses in a single institution phase II study showed that fixed-dose rate gemcitabine at 10mg/m^2/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 with leiomyosarcoma [23].

The single-institution study of fixed-dose rate gemcitabine plus docetaxel yielded high objective response rates among patients with advanced leiomyosarcoma in both the second-line, and first-line setting [23]. More recently, fixed-dose rate gemcitabine plus docetaxel has been shown to yield higher response rates, progression-free, and overall survival (OS) than fixed-dose rate single agent gemcitabine in a randomized trial for patients with soft tissue sarcoma who had received up to three prior regimens [24]. In a Gynecologic Oncology Group (GOG) phase II trial for women with advanced leiomyosarcoma who had received one prior cytotoxic regimen, fixed-dose rate gemcitabine plus docetaxel achieved objective response in 28% of patients, with an additional 50% having stable disease [25].

Given the evidence for efficacy in the second-or-greater-line setting, the GOG sought to determine the objective response rate of fixed-dose rate gemcitabine plus docetaxel among women with advanced, unresectable uterine leiomyosarcoma who had received no prior cytotoxic therapy.

MATERIALS AND METHODS

Patients

Women with advanced, unresectable uterine leiomyosarcoma, with measurable disease and no prior cytotoxic therapy were eligible. All tumors were histologically confirmed 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 × institutional upper limit of normal); hepatic function (bilirubin less than or equal to 1.5 × institutional upper limit of normal, and Serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase less than or equal to 2.5 × institutional upper limit of normal); and neurologic function (baseline neuropathy, sensory and motor, less than or equal to Common Toxicity Criteria grade 1). Patients with a history of other invasive malignancy within the past five years were not eligible.

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

Treatment

All participants had baseline imaging (Computed Tomography (CT) scan of chest, abdomen, and pelvis) within four weeks of starting therapy. CT imaging was repeated following every other cycle of treatment to assess response. History and physical examination, and assessment of toxicities were done at 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/m^2 on days one and eight intravenously over 90 minutes, followed by docetaxel 100 mg/m^2 on day eight intravenously over one hour. Granulocyte-colony-stimulating factor (GCSF) 150 microgram/m^2 was given subcutaneously on days nine through 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/m^2 on days one and eight intravenously over 90 minutes, followed by docetaxel 75 mg/m^2 on day eight intravenously over one hour, with the same granulocyte growth factor support as above. Treatment cycles were repeated approximately every three weeks, and patients continued on study until time of progression or unacceptable toxicity.

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 per cent 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 it was within institutional normal limits. Day eight treatment with docetaxel was omitted if the bilirubin remained 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, Serum glutamic pyruvic transaminase (SGPT), or alkaline phosphatase; and treatment was not resumed until such grade 3 elevations had resolved to grade 1 or less.

Patients who experienced 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.

Assessment of Toxicity and Response

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

All patients who received at least one cycle of study treatment were considered assessable for response. 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 is any condition not meeting the above criteria. All 42 patients enrolled on study were included in the assessment of response.

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, 12−19 patients were to be entered and evaluated. If at least two responses were observed among the first 12−14 patients, or at least three responses out of 15−19 patients, a second phase of accrual was to be initiated which would increase accrual to 36−43 patients. The regimen would be considered active if at least seven responses were observed among 36−39 patients, or at least eight responses were observed among 40−43 patients. If the true response rate is 10%, the average probability of designating the treatment as active is limited to 10%. Conversely, if the true response rate was 30%, then the probability of correctly classifying the treatment as active was 90%.

RESULTS

Between December 2003 and June 2006, 42 women were enrolled in this phase II study from 24 GOG participating institutions. Three patients were considered inevaluable for objective response (one patient declined further treatment or follow-up imaging after day one treatment with gemcitabine alone; one patient had immediate hypersensitivity reaction to docetaxel on cycle one day eight and declined further treatment or imaging after cycle 1; one patient received gemcitabine on cycle 1, day one and was non-compliant with appointments for day eight treatments). However, all 42 patients are included in the calculation of objective response rate.

The first phase of accrual (19 patients) was achieved in 12 months. After assessment of response was completed, the study re-opened in May 2005 and the second stage of accrual was achieved over the next 12 months. Thus accrual goals were met with 24 months of active accrual time.

The median age of the cohort was 56.3 years (range 33−73). Ninety percent had a GOG performance status of 0 or 1, 10% had performance status 2. Twelve patients (29%) had prior pelvic radiation for leiomyosarcoma. The median number of cycles of study treatment delivered per patient was 4 (range 1−15). Details of the patient cohort are given in Table 1.

Response and survival

RECIST-measured objective response was observed in 15 of the 42 patients enrolled (35.8%). Two patients had complete clinical response (4.8%), and 13 met RECIST for confirmed partial response (31%). Eleven of 42 (26.2%) had stable disease. Response rates are summarized in Table 2.

Among all 42 patients, the median PFS was 4.4 months (range 0.4 to 37+ months). Among the 15 patients with objective response, the median duration of response was six months (range 2.1 to 33.4+ months). The median duration of stable disease was 4.3 months, (range: 2.1 to 17.2+ months). The percentage of patients remaining progression-free at 12 weeks and 24 weeks was 59.5% and 40.5%, respectively. PFS is shown in Figure 1; the median OS is 16.1 + months (range: .4 − 41.3 months)

Toxicity

Toxicities observed with study treatment are summarized in Table 3. Myelosuppression was the major toxicity: neutropenia grade 3 in 5%, grade 4 in 12%; anemia grade 3 in 24%, grade 4 in none; thrombocytopenia grade 3 in 9.5%, grade 4 in 5%. There were no episodes of neutropenic fever. 43% of patients received packed red blood cell transfusions, and 5% received platelet transfusions.

Hypersensitivity to docetaxel is a known potential toxicity, and one patient had a grade 3 allergic reaction. Grade 3 fatigue was reported by 17% of patients. Gastrointestinal toxicity (nausea) was reported in 12% and grade 4 in one patient (2%). Pulmonary toxicity was seen in one patient: grade 4 hypoxia requiring intubation occurred on day 18 of cycle 12 of study treatment. CT imaging showed stable pulmonary metastases and radiation changes, and new infiltrates. She was treated for possible pneumocystis carinii pneumonia and improved, such that extubation was possible six days later. She came off study treatment for this possibly-related toxicity. Her best response had been PR.

DISCUSSION

Doxorubicin has been the backbone of first-line therapy for unresectable soft tissue sarcoma for decades, and continues to be recommended by sarcoma treatment guidelines [27]. High objective response rates in phase II trials of fixed-dose rate gemcitabine plus docetaxel as second-or-greater line therapy in leiomyosarcoma led to this cooperative group, multi-institution study testing the activity of this regimen as first-line therapy for unresectable uterine leiomyosarcoma [25,28]. Objective responses were observed in 35.8% of all patients enrolled on study, with an additional 26.2% having minor responses or stable disease. This first-line response rate compares favorably with response rates seen with doxorubicin, gemcitabine, and other single-agent and combination-agent regimens tested in phase II trials [4,29]. While the objective response rate of 35.8% is somewhat lower than the 50% response rate reported from the single-institution phase II study of this regimen, a discrepancy of this magnitude is not unexpected when regimens are tested in the cooperative group, multi-institution setting.

The toxicity of fixed-dose rate gemcitabine plus docetaxel is primarily myelosuppression. Seventeen percent of patients had grade 3 or 4 neutropenia, however, there were no episodes of neutropenic fever. One-quarter of patients had grade 3 anemia, and 10% had grade 3 or 4 thrombocytopenia, but there were no significant bleeding events. While the frequencies of neutropenia and anemia are similar to those seen in the GOG study of fixed-dose gemcitabine plus docetaxel as second-line therapy, the frequency of thrombocytopenia was much lower in this study of the regimen as first-line treatment, most likely reflecting the effects of prior chemotherapy on bone marrow reserves among patients in the second-line study [25]. In addition, the percent of patients who had prior pelvic radiation was somewhat higher in the second-line study (35%) than in this first-line study (29%), which may have also influenced the frequency of myelosuppression. One patient experienced grade 4 pulmonary toxicity. She was treated for pneumocystis carinii pneumonia and improved. However, the clinical picture is also potentially consistent with the pneumonitis-type pulmonary toxicity described with both gemcitabine and docetaxel, thus we considered this event possibly treatment-related. [7-10, 30-33].

Fixed-dose rate gemcitabine as a single agent was compared to fixed-dose rate gemcitabine plus docetaxel in a randomized trial for patients with soft tissue sarcoma and 0−3 prior regimens [24]. In that study, gemcitabine plus docetaxel treatment was associated with higher rates of response, and longer progression-free survival (6.2 months) and OS (18 months) compared to gemcitabine alone. The response rates, PFS and OS in this GOG phase II study of gemcitabine plus docetaxel for uterine leiomyosarcoma compare favorably with those results. The percentage of patients remaining progression-free at 12 weeks and 24 weeks may be regarded as a reasonable indicator of treatment activity [34]. Treatment regimens associated with 39% of patients progression-free at 12 weeks, and 14% progression-free at 24 weeks are considered to be active in soft tissue sarcoma [34]. First-line treatment of uterine leiomyosarcoma with fixed-dose rate gemcitabine plus docetaxel exceeded these criteria, with 60% of patients progression-free at 12 weeks and 40% of patients progression-free at 12 weeks.

It has been suggested that patients with leiomyosarcoma may have a higher chance of responding to cytotoxic chemotherapy than do patients with other soft tissue sarcoma histologies. A retrospective study evaluated responses to gemcitabine plus docetaxel among patients with soft tissue sarcoma treated outside of a clinical trial setting. In that study, the overall response rate was 18.3% among 133 patients [35]. The response rate among the subset of patients with leiomyosarcoma was 24% compared with 10% for patients with non-leiomyosarcoma histology (p=0.06). This response rate among leiomyosarcoma patients is comparable to the response rates seen among uterine leiomyosarcoma patients treated in the GOG study of second-line gemcitabine-docetaxel (objective response 27%), and in this GOG study of first-line therapy (objective response 35.8%) [25].

As first line treatment for unresectable uterine leiomyosarcoma, fixed-dose rate gemcitabine achieves objective response in more than one-third of patients. The median duration of objective response was six months. Fixed-dose rate gemcitabine plus docetaxel is a reasonable option for first line treatment of uterine leiomyosarcoma.

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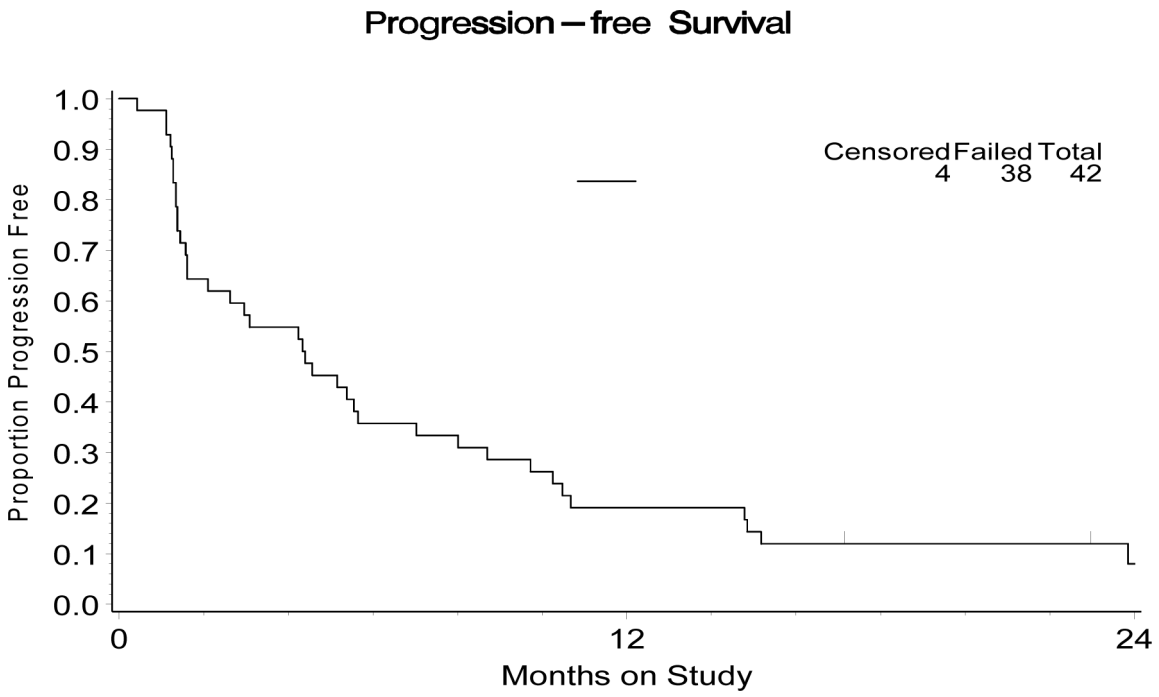

Figure 1.
Progression-free survival for patients with advanced leiomyosarcoma (n=42). Median progression-free survival is 4.4 months, range (range: 0.4 to 37.2 + months)

Table 1

Patient Characteristics (n=42)

Characteristic	Number of Patients
Age	
<40	2
40−49	10
50−59	15
60−69	13
>69	2
Performance Status	
0	23
1	15
2	4
Race	
White	31
Black	7
American Indian	2
Unspecified	2
Prior Chemotherapy	0
Prior Radiotherapy	12
Cycles of study treatment received	
1	2
2	13
3	3
4	4
5	1
6	5
≥ 7	14

Table 2

RECIST-defined responses to treatment (n=42)

Response Category	Number of Patients	%
Complete Response	2	4.8
Partial Response	13	31.0
Stable Disease	11	26.2
Increasing Disease	13	28.4
Inevaluable for objective response*	3	9.6
Total number of patients	42	100

* Although response could not be determined in three cases (one patient declined further treatment or follow-up imaging after day one treatment with gemcitabine alone; one patient had immediate hypersensitivity reaction to docetaxel on cycle one day eight and declined further treatment or imaging after cycle 1; one patient received gemcitabine on cycle 1, day one and was non-compliant with appointments for day eight treatments), all 42 patients are included in determination of response rate.

Table 3

Adverse events considered at least possibly related to study treatment, all grades, by number of patients experiencing the event.

	Grade					
Adverse Event	**0**	**1**	**2**	**3**	**4**	**Total**
Leukopenia	18	10	8	3	3	42
Thrombocytopenia	9	22	5	4	2	42
Neutropenia	27	2	6	2	5	42
Anemia	0	7	25	10	0	42
Other hematologic	33	4	3	2	0	42
Coagulation	40	1	0	1	0	42
Hemorrhage	38	2	2	0	0	42
Allergic reaction	33	5	3	1	0	42
Dermatologic	11	3	27	1	0	42
Auditory	40	0	2	0	0	42
Fatigue	11	15	9	7	0	42
Gastrointestinal	12	12	12	5	1	42
Genitourinary/Renal	36	3	3	0	0	42
Hepatic	35	7	0	0	0	42
Infection	30	3	8	1	0	42
Metabolic[1]	21	5	9	7	0	42
Lymphocytes	33	5	4	0	0	42
Musculoskeletal	38	3	0	1	0	42
Neurotoxicity	32	7	2	1	0	42
Peripheral neuropathy	33	7	2	0	0	42
Ocular[2]	35	4	3	0	0	42
Pain	23	12	5	1	1	42
Pulmonary[3]	32	6	3	0	1	42
Cardiovascular[4]	37	4	0	1	0	42
Constitutional[5]	28	4	10	0	0	42
Endocrine	40	1	1	0	0	42
Hospitalization	40	2	0	0	0	42

The median white blood count for those 24 patients experiencing leukopenia was 2950 (range: 700−3700). The median platelet nadir for those 33 patients experiencing thrombocytopenia was 87,000 (range: 11,000−131,000).

[1] metabolic toxicities included: hyponatremia, hypokalemia, hyperglycemia, hypoalbuminemia, and elevations in AST or ALT.

[2] Ocular toxicities included tearing (epiphora), periorbital edema, photophobia, and blurred vision.

[3] The grade 4 event occurred after cycle 12 and was possibly related to study treatment.

[4] Cardiovascular toxicity, grade 3, was a deep venous thrombosis

[5] Constitutional symptoms, other than fatigue, included weight loss, and fever without infection, at least possibly related to study treatment.

Table 4

Summary table of response rates in GOG phase II trial of various chemotherapy agents in advanced uterine leiomyosarcoma.

GOG phase II study principal investigator, reference	Drug	# prior regimens	Objective Response rate
McMeekin[19]	thalidomide	1	0/29 **(0%)**
Look[27]	gemcitabine	0−1	9/42 **(20%)**
Sutton[3]	liposomal doxorubicin	0	5/32 **(16%)**
Gallup[17]	paclitaxel	0−1	4/48 **(8%)**
Sutton[18]	paclitaxel	0	3/33 **(9%)**
Thigpen[16]	cisplatin	0	1/33 **(3%)**
Sutton[3]	doxorubicin	0	7/28 **(25%)**
Sutton[5]	ifosfamide	0	6/35**(17%)**
Thigpen[34]	etoposide IV	0	0/28 **(0%)**
Rose[13]	etoposide PO	1	2/29 **(7%)**
Miller[16]	topotecan	0	4/36 **(11%)**
Smith[20]	trimetrexate	0−1	1/23 **(4%)**
GOG 87L (Hensley) *	gemcitabine + docetaxel	0	15/42 **(36%)**

* GOG 87L is the study whose results are the subject of this report.