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Adjuvant gemcitabine plus docetaxel for completely resected stages I–IV high grade uterine leiomyosarcoma: Results of a prospective study ☆

Martee L. Hensley [a,*], Nicole Ishill [b], Robert Soslow [c], Joseph Larkin [a], Nadeem Abu-Rustum [d], Paul Sabbatini [a], Jason Konner [a], William Tew [a], David Spriggs [a], Carol A. Aghajanian [a]

[a] Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
[b] Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
[c] Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
[d] Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065. USA

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ABSTRACT

Objective. Patients with completely resected stages I–IV high grade uterine leiomyosarcoma are at high risk for recurrence. No adjuvant treatment has been shown to improve survival, although prospective data are limited. We sought to determine whether adjuvant gemcitabine-docetaxel would yield a 2-year progression-free survival of at least 50% in this leiomyosarcoma population.

Methods. Eligible patients were treated with gemcitabine 900 mg/m^2 over 90 min days 1 and 8 plus docetaxel 75 mg/m^2 day 8, every 3 weeks for 4 cycles. CT imaging was performed at baseline, after cycle 4, and every 3 months. Progression was defined as evidence of new disease on CT.

Results. Twenty-five patients (median age 49; range, 37–73) enrolled; 23 were evaluable (1-never treated, 1-ineligible). With median follow-up of 49 months for all patients, 10 (45%) of the 23 evaluable patients remained progression free at 2 years, with a median progression-free survival of 13 months. The median overall survival is not yet reached. Among the 18 patients with stages I or II uterine leiomyosarcoma, 59% remain progression-free at 2 years, with a median progression-free survival of 39 months. Median overall survival for stages I and II patients is not yet reached with median follow-up duration of 49 months. Sites of first recurrence were: lung only — 3/23 (13%); pelvis only — 5/23 (22%); both — 5 (22%).

Conclusions. Post-resection gemcitabine-docetaxel for stages I–IV high-grade uterine leiomyosarcoma yields 2-year progression-free survival rates that appear superior to historical rates. Gemcitabine-docetaxel merits further study as part of an adjuvant strategy for patients with completely resected, early-stage uterine leiomyosarcoma.

Introduction

Uterine leiomyosarcoma is a rare malignancy with fewer than 2000 cases per year in the United States. The majority of women present with tumor that is limited to the pelvis at the time of diagnosis. Although complete resection is frequently accomplished, the risk for recurrence after complete resection of FIGO stage I (tumor confined to the uterus) or II (tumor in uterus and cervix) high grade uterine leiomyosarcoma is 50–80% at 2 years [1–4]. The risk of recurrence is greater for patients with higher-stage disease, and likely is greater for tumors with higher mitotic rates [5,6], although no standard prognostic criteria have been established.

Although the risk for recurrence is high, no adjuvant treatment strategy is considered standard since there are no trials demonstrating that adjuvant treatment improves progression-free or overall survival, compared with surgical resection alone. A recent randomized phase III trial of adjuvant pelvic radiation versus observation for stages I and II uterine sarcomas (carcinosarcoma, leiomyosarcoma or endometrial stromal sarcoma) showed that pelvic radiation did not improve outcomes for the patients with leiomyosarcoma in terms of local control, progression-free, or overall survival [7]. Only one randomized trial of adjuvant chemotherapy versus observation for resected stages I and II uterine leiomyosarcoma has been completed. In that Gynecologic Oncology Group study, 156 evaluable women with uterine sarcomas of various histologies (leiomyosarcoma, carcinosarcoma, or other) were randomly assigned to 8 cycles of doxorubicin or observation [8]. In the subgroup of patients with leiomyosarcoma (n=48) the recurrence rate was 61% among patients assigned to observation versus 44% among patients assigned to doxorubicin. Interpretation and application of these data are limited by the mixed histology population, the non-random use of adjuvant pelvic radiation, and the lack of protocol-specified imaging for disease status.

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* Corresponding author. Fax: +1 212 717 3214.
E-mail addresses: gynbreast@mskcc.org, kblaser@gogstats.org (M.L. Hensley).

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Fixed-dose rate gemcitabine plus docetaxel achieves high objective response rates in patients with advanced, recurrent uterine leiomyosarcoma as first- or second-line therapy [9–11]. Given the activity of this regimen in advanced disease, we sought to determine whether fixed-dose rate gemcitabine plus docetaxel might have a potential role as adjuvant treatment for completely resected uterine leiomyosarcoma. This study was designed as a single-arm phase II study to determine the two-year progression-free survival among women with completely resected stages I–IV uterine leiomyosarcoma who were treated with adjuvant fixed-dose rate gemcitabine plus docetaxel. Since historical data suggested that approximately 30% of patients with resected stages I–IV high grade uterine leiomyosarcoma remained progression-free at 2 years [12–14], observation of a two-year progression-free survival rate of at least 40%, would merit consideration of adjuvant fixed-dose rate gemcitabine plus docetaxel for further study as adjuvant therapy for stages I and II uterine leiomyosarcoma.

Methods

Patient eligibility

Women aged 18 or older, with histologically confirmed high grade leiomyosarcoma of the uterus, FIGO stages I, II, III, or IV, which had been completely resected within 8 weeks of enrollment, were eligible. Tumors meeting histologic criteria for leiomyosarcoma [15] were considered high grade. Patients must not have received prior chemotherapy for treatment of leiomyosarcoma or prior whole pelvic radiotherapy. Patients must have had no evidence of disease on post-resection CT scan imaging of the chest, abdomen, and pelvis performed within 4 weeks of enrollment. Patients were required to have adequate organ function as evidenced by the following: absolute neutrophil count ≥1000/μL, platelet count ≥100,000/μL, serum creatinine ≤2.0 mg/dL, total serum bilirubin within institutional normal limits; transaminases (ALT and AST) could be up to 2.5 times institutional upper limit of normal (ULN) if alkaline phosphatase is ≤ULN, or alkaline phosphatase could be up to 4 times ULN if transaminases are ≤ULN), Karnofsky performance status ≥70%, and no peripheral neuropathy worse than grade 1 at baseline. Pregnant or lactating women, and patients with active uncontrolled infection, or history of prior malignancy, were excluded. Patients were not permitted to receive adjuvant pelvic radiation as part of their post-resection treatment.

All patients signed written, informed consent. The protocol was approved by the Institutional Review Board, and reviewed annually.

Treatment plan

Participants received gemcitabine 900 mg/m^2 on days 1 and 8 intravenously over 90 min, followed by docetaxel 75 mg/m^2 on day 8 intravenously over 1 h. The recommended pre-medication for the docetaxel was dexamethasone 8 mg orally for 2 doses the day prior to chemotherapy, and 8 mg orally twice daily for the next 2 days. Patients who developed peripheral edema as a side effect of docetaxel were treated with diuretics at the discretion of the treating physician.

Recombinant human granulocyte-colony stimulating factor (GCSF) 150 μg/m^2 (dose rounded to 300 μg or 480 μg) was given subcutaneously on days 9–15, or pegylated filgrastim 6 mg on day 9, as primary neutropenia prophylaxis. Treatment cycles were administered in the outpatient setting every 3 weeks for a total of 4 cycles. Day one and day eight treatment was given provided the absolute neutrophil count was ≥1000/μL and platelet count ≥100,000/μL. Day eight treatment was given at 75% of planned dose if absolute neutrophil count was between 500–1000/μL or the platelet count was between 50,000–100,000/μL. If blood counts failed to recover after treatment hold of up to 2 weeks, the patient was removed from study treatment. Dose reductions or treatment interruptions were also required for significant liver dysfunction, peripheral neuropathy, stomatitis, or hypersensitivity reactions.

Evaluations during treatment

Pre-treatment evaluations included: history and physical examination, complete blood count with differential and platelet count, biochemical profile, electrocardiogram, chest X-ray, and CT scan of the chest, abdomen, and pelvis. During treatment, complete blood cell counts were performed approximately weekly and serum chemistries every 3 weeks. History and physical examinations and assessment of toxicities were performed prior to each cycle of treatment. CT scan of the chest, abdomen, and pelvis was performed at the end of cycle 4 and then every 3 months for 2 years, then every 6 months for 3 years, then annually.

Statistical considerations

Toxicities were graded according to National Cancer Institute Common Toxicity Criteria version 2.0 [16]. An estimate of the potential efficacy of the adjuvant strategy was to be based on the percentage of patients observed to remain progression-free at 2 years from enrollment. The study was originally designed to enter 39 patients. If 16 or more (41%) survived 2 years progression-free, then the adjuvant treatment strategy was to be considered sufficiently promising for further development. The likelihood of observing 16 or more patients out of 39 to remain progression-free at 2 years is 90% if the true 2-year PFS probability is .50, and 10% if the true PFS probability is .30. The study included an early stopping rule for unacceptable toxicity such that the study would be stopped if eight grade 3 or 4 non-hematologic, at least possibly-related, toxicities were observed. The study was closed early, after enrollment of 23 evaluable patients, as the progression-free survival rate appeared promising, and, thus, a national, multi-institution study incorporating the fixed-dose rate gemcitabine plus docetaxel regimen as adjuvant therapy for stages I and II uterine sarcoma was being opened, and we wished to participate in the larger, national study.

Results

Patient demographics

Twenty-five patients (median age, 49; range, 37–73) were enrolled between July 2002 and January 2006, with patient details summarized in Table 1. Twenty-three were evaluable (1 — never treated, 1 — ineligible) for progression-free survival. FIGO stage distribution was stage 1: 15 (65%), stage II: 3 (13%), stage III: 1 (4%), stage IV: 4 (17%). All patients had had at least a total abdominal hysterectomy; one or both ovaries remained in place in three patients; surgery included lymph node sampling or dissection in ten patients. The average tumor mitotic

Table 1
Demographics of patients with high grade uterine leiomyosarcoma treated with adjuvant gemcitabine plus docetaxel (n=23)

Patient and tumor characteristics		
Patient age, years	Median 49	Range 37–73
Stage I (number of patients, percent)	15	65%
Stage II	3	13%
Stage III	1	4%
Stage IV	4	17%
Tumor mitotic rate	Median 20 mitoses/10 high-power fields	Range 5–60 mitotses/ 10 high-power fields
Tumor size for stages I and II patients (n=18)	Median 10 cm	Range 6–28 cm