



Case series

A randomized phase II study of letrozole vs. observation in patients with newly diagnosed uterine leiomyosarcoma (uLMS)

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ARTICLE INFO

Keywords:

Leiomyosarcoma
Letrozole

ABSTRACT

Objective: Up to 87% of uterine leiomyosarcomas have estrogen receptor positivity. There are no effective adjuvant therapies for LMS. The objective of this study was to determine the efficacy of letrozole in patients with newly diagnosed uterine leiomyosarcoma (uLMS). The primary endpoint of this study was a reduction in the recurrence rate for patients with this disease.

Methods: We performed a randomized, open-label, phase II study of letrozole (experimental arm) administered orally on a daily basis vs. observation (control) in patients with newly diagnosed early stage uLMS. Patient enrollment was to be open to any individual with newly diagnosed uLMS seen in the Gynecologic Oncology Center at M. D. Anderson Cancer Center. Hormone receptor positivity using CLIA approved lab testing was an eligibility requirement. No prior therapy was allowed.

Results: Nine patients were randomized. Four patients were in the experimental arm and five patients were in the observation arm. No patients had prior therapy. The median duration of protocol treatment was 43.9 months (range, 6.5–70.2). The median PFS for the experimental arm was not reached (NR) compared to 17.3 months. The percent progression free at 12 and 24 months was 100% for patients receiving letrozole compared to 80% at 12 months and 40% at 24 months for patients in the observation arm.

Conclusions: While no definitive conclusions can be made due to early study closure, these early observations warrant further investigation. We desperately need an effective adjuvant therapy for women with early stage uLMS.

1. Introduction

Uterine leiomyosarcomas (uLMS) are rare, accounting for < 5% of all malignant uterine neoplasms (Platz and Benda, 1995; Zivanovic et al., 2009; Mayerhofer et al., 1999). Despite the low incidence of high stage disease, approximately 50% of patients will recur within two years (Hensley et al., 2009; Giuntoli et al., 2003; Hornback et al., 1986; Omura et al., 1985; Major et al., 1993). Most of these patients recur outside of the pelvis (Mayerhofer et al., 1999; Major et al., 1993).

The role of adjuvant therapy in uLMS has been studied using both radiation and/or chemotherapy. The Gynecologic Oncology Group (GOG) evaluated the role of adjuvant radiation therapy in patients (n = 48) with stage I and II disease. Forty-eight percent of the patients recurred and most of these patients recurred within 17 months of diagnosis (Hornback et al., 1986). There was no difference in the progression-free interval, absolute two-year survival rate, or site of first

recurrence between patients who received pelvic radiation (n = 11) and those that did not (n = 37). In another GOG study, early stage uLMS patients were randomized to adjuvant chemotherapy or no further treatment (Omura et al., 1985). In the patients (n = 75) treated with doxorubicin, 44% recurred compared to 61% in patients who did not receive chemotherapy. Similar to radiation therapy, there was no improvement in progression-free interval or survival with use of adjuvant chemotherapy.

GOG-277 enrolled patients with stage I uterine-confined LMS, and compared patients who received adjuvant gemcitabine/docetaxel for 4 cycles followed by doxorubicin for 4 cycles to patients in an observation group. The primary endpoint was overall survival (OS), however, the study closed early due to low accrual. Twenty patients were enrolled in the experimental arm, and 18 patients were enrolled in the observation arm. Over 48 months, the restricted mean survival time (RMST) for OS was estimated to be 34.3 months (95% CI:

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<https://doi.org/10.1016/j.gore.2018.11.001>

Received 10 October 2018; Received in revised form 2 November 2018; Accepted 6 November 2018

Available online 16 November 2018

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Table 1A
Letrozole patients.

Acc	Treatment start date	Treatment end date	Days on treatment	Reason off treatment	Date of progression (Status: Date of last follow-up)	Days till progression
1	01/31/07	12/05/12	2136	MD decision after 5 yrs. of tx and NED	NED (06/15/16)	
5	08/09/07	12/11/10	1221	Progression	12/13/10 (DOD: 09/13/13)	1223
6	01/14/08	01/03/12	1451	Patient decision, moved to Florida	NED (08/17/16)	
9	01/15/10	07/30/10	197	Toxicity, moved to Florida and Lost to FU	NED (04/02/13)	

NED: No evidence of disease, AWD: Alive with disease.

Table 1B
Observation patients.

Acc	On study date	Follow UP date	Off study date	Reason off study	Date of progression (Status: Date of last follow-up)	Days till progression
2	02/20/07		08/13/08	Progression	07/22/08 (DOD: 03/15/09)	519
3	04/26/07		04/07/10	Withdrew - due to frequency of scans	NED (8/11/16)	
4	06/25/07		02/27/08	Withdrew - due to frequency of scans	05/18/09 (AWD: 05/02/17)	694
7	03/26/08		09/03/08	Progression	09/02/08 (DOD: 09/02/12)	161
8	04/21/09		04/17/12	Withdrew voluntarily after NED for 3 yrs	NED (05/12/16)	

NED: No evidence of disease.

Table 2
Reason off-treatment, progressive disease, and follow-up duration.

N		Letrozole	Observation
		4	5
Reason off treatment	Progressive disease	1	2
	Other	3	3
Progressive disease	No	3	2
	Yes	1	3
Follow-up months (median)		37.8	48.9

43.6–49.1 months) for the combination chemotherapy arm, and 46.4 months (95% CI: 43.6–49.1 months) for the observation arm, favoring the observation arm. Over 24 months, the RMST for recurrence free survival (RFS) was estimated to be 18.1 months (95% CI: 14.2–22.0 months) for the combination chemotherapy arm, and 14.6 months (95% CI: 10.3–19.0 months) for the observation arm. Though GOG-277 closed early, the observed OS and RFS do not suggest superior outcomes for patients treated with adjuvant gemcitabine/docetaxel followed by doxorubicin. (Hensley et al., 2018)

Unlike other gynecologic malignancies, where the recurrence rate is highest over the first 12–18 months, the risk of recurrence in patients with early stage LMS is linear and consistent over several years. (Major et al., 1993) With this pattern of recurrence, one reasonable approach would be to develop a treatment strategy that can be maintained throughout this risk period. A treatment that is well tolerated with minimal toxicity with good efficacy is needed. Forty to 87% of leiomyosarcomas express the estrogen receptor (ER) and 38–80% express the progesterone receptor (PR). (Leitao et al., 2004; O'Cearbhaill et al., 2010; Akhan et al., 2005; Kelley et al., 2004) Estrogen may act as a growth factor that stimulates cell proliferation and tumor growth. (Leitao et al., 2012)

Given the relatively high rate of hormone receptor positivity for LMS, we hypothesized that by decreasing systemic estrogen using an aromatase inhibitor, we can prolong the time to recurrence for patients with this disease. Herein, we report our phase II trial of letrozole (Femara, Novartis) vs. observation for the treatment of newly diagnosed uLMS.

2. Patients and methods

We designed and conducted an open-label phase II, randomized trial

Table 3
Toxicity.

Toxicity	Grade				
	1	2	3	4	5
Alopecia	1	0	0	0	0
Arthralgia	0	1	0	0	0
Bilirubin	1	0	0	0	0
Cholesterol	2	0	0	0	0
Constipation	1	0	0	0	0
Diarrhea	1	1	0	0	0
Fatigue	0	2	1	0	0
Fever without neutropenia	0	1	0	0	0
Hot flashes	4	0	0	0	0
Insomnia	0	1	0	0	0
Memory impairment	1	0	0	0	0
Mood alteration (depression)	1	0	1	0	0
Myalgia	1	0	0	0	0
Nausea	0	0	1	0	0
Neuropathy: sensory	0	1	0	0	0
Pain (joint)	0	0	1	0	0
Pain (muscle)	1	1	0	0	0
Pruritus/itching	1	0	0	0	0
Tinnitus	1	0	0	0	0
Vaginal dryness	0	1	0	0	0
Totals	16	9	4	0	0

of letrozole vs. observation for newly diagnosed uterine leiomyosarcoma in the Department of Gynecologic Oncology and Reproductive Medicine at the University of Texas M.D. Anderson Cancer Center from January 2007 to January 2010. The primary objective of this study was to evaluate the efficacy of letrozole in patients with uterine LMS. The primary endpoint of this study was progression-free survival (PFS). Secondary endpoints included overall survival (OS), safety, and tolerability. Institutional review board approval was obtained.

2.1. Patient population

Patients with histologically confirmed uLMS with disease limited to the uterus on hysterectomy specimen, expressing > 10% ER positivity by immunohistochemistry, and a Zubrod performance status of 0 to 2 were eligible. Women who did not have pure uterine sarcomas were excluded. The study also required that women have no history of prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the

patient had been disease-free for at least five years before trial entry, no measurable disease (defined as lesions that can be measured by physical examination or by means of imaging techniques), not be of child-bearing potential (or that they had a negative pregnancy test within seven days of treatment), not be breast feeding, and that they had recovered from the effects of prior surgery.

Pretreatment hematologic parameters included, granulocyte count (i.e., segmented neutrophils + bands) of $> 1000/\text{Fl}$, a hemoglobin level of $\geq 9.0 \text{ g/dL}$, and a platelet count of $> 75,000/\text{Fl}$. Patients were required to have an adequate renal function (serum creatinine $\leq 2.0 \text{ mg/dL}$), and hepatic function (serum bilirubin $\leq 2.5 \text{ mg/dL}$), regardless of whether patients had liver involvement secondary to their tumor. Aspartate transaminase (SGOT) was required to be $\leq 3 \times$ the institutional upper limit of normal unless the liver was involved with the tumor. In that case, the aspartate transaminase was required to be $\leq 5 \times$ the institutional upper limit of normal.

Other exclusion criteria included any severe concurrent disease which would have made the patient inappropriate for study entry, including significant hepatic, renal, or gastrointestinal diseases; using letrozole or another aromatase inhibitor at the time of diagnosis of the leiomyosarcoma; active or uncontrolled systemic infection; a history of uncontrolled cardiac disease, including uncontrolled hypertension, unstable angina, recent myocardial infarction (within the prior six months), uncontrolled congestive heart failure, and cardiomyopathy with an ejection fraction under 40%; clinically apparent untreated central nervous system metastases or carcinomatous meningitis; presence of deep venous or arterial thrombosis (including pulmonary embolism) within six weeks of study entry (however, maintenance anticoagulation therapy was permitted); HIV positive patients; patients receiving chemotherapy or radiation therapy at the time of trial initiation.

2.2. Treatment plan and response evaluation

The dose of letrozole 2.5 mg (tablets) daily was given orally with no dose modifications. Women randomized to the letrozole arm were treated on an outpatient basis and remained on the study until disease progression, drug-related toxicity, being lost to follow-up, voluntary withdrawal, or until discontinuation after a prolonged disease-free interval at the treating physician's discretion.

All patients were to be followed for at least 24 months following treatment allocation to the experimental (letrozole) or control arm (observation). The primary efficacy endpoint was progression-free survival. Imaging and physical examination were to be repeated every three months for two years, and then every six months thereafter.

Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

2.3. Estrogen receptor testing

Estrogen positivity was defined as 10% or greater staining as evaluated by IHC. IHC testing was done using commercially available results from CLIA-approved pathology labs.

2.4. Statistical design

We planned to accrue a minimum of 10 patients and a maximum of 80 patients at a rate of 2 patients per month. The primary outcome was progression-free survival (PFS) or death. Our target median progression-free survival was 24 months. (Major et al., 1993) All patients were to be followed for at least 24 months following treatment allocation.

Patients were randomized between standard of care and experimental treatments using a Bayesian adaptive algorithm. (Berry and Eick, 1995) The first 10 patients were to be randomized equally between the two treatment arms. The intent of the adaptive randomization was to balance the treatment allocation in favor of the arm that, on average,

has better results in terms of PFS, so that each successive patient would be more likely to receive the treatment showing better results. The trial was designed to stop early and a treatment selected as being “better” if the probability was 0.90 or higher that one treatment arm produced a PFS that was longer than the other. Under the statistical assumptions, if all 80 patients were enrolled, then a treatment being selected as “better” would be 0.80 or more.

The statistical methodology was designed to result in early termination if, based on the available data, there was low probability that the median progression-free survival for the experimental treatment was at least 24 months. Specifically, we specified the following term $\Pr(\text{median progression-free survival} \geq 24 \text{ months} \mid \text{data from the trial}) < 0.125$ for early study discontinuation, implying that if there was less than a 12.5% chance that the median progression-free survival was at least 24 months, then we would stop further enrollment. We assumed that patients would be accrued at a rate of 1.5 per month, and that we would be evaluating the monitoring rule continually. Once the trial completed, an estimate of the time to local recurrence would be conducted in the Kaplan-Meier method. (Kaplan and Meier, 1958) We also planned to report the posterior probability that the median progression-free survival was at least 24 months, giving a 90% credible interval for the median progression-free survival.

3. Results

3.1. Patients

A total of nine patients were enrolled onto the trial between January 2007 and January 2010. The follow-up period for the letrozole arm spanned from October 2010 through August 2016. The follow-up period for the observation arm began in May 2007 and ended in May 2017. Four patients were treated with letrozole. Five patients were in the observation group. Toxicity and efficacy were evaluated for all patients. The median patient age was 49.7 years (range, 38–60). Study patients received a total of 178.8 cycles of therapy, and a median of 47.7 cycles. Each cycle consisted of 28 days. All nine enrolled patients had a Zubrod Performance status of 0.

3.2. Efficacy

In the treatment arm, three patients had no evidence of disease (NED) at last contact. One of these patients was taken off of therapy at the discretion of their clinician after 5 years of treatment and NED. One patient was NED at the time that they voluntarily withdrew from the study. One patient was NED at the time that they were lost to follow-up. One patient was taken off treatment due to progression, and ultimately died of disease.

Of the five patients assigned to the observation arm, two patients died of disease. Two patients, both NED at the time of last contact, voluntarily withdrew from the study. Another patient, who was AWD at time of last contact, also withdrew.

Median PFS for the experimental and observation arms were not reached (NR) vs. 519 days (approximately 17 months), respectively. Median OS could not be calculated due to lack of follow-up data. The rate of progression for the experimental arm at both 12 and 24 months was 0% (i.e. the percent progression free at 12 and 24 months was 100%). The rate of progression for the observation arm at 12 and 24 months was 20% and 60%, respectively (i.e. the percent progression free for the observation arm at 12 and 24 months was 80% and 40%).

3.3. Safety

For the experimental arm, there were no Grade 4 Toxicities reported and only four Grade 3 toxicities reported (fatigue, mood alteration-depression, nausea, and joint pain).

3.4. Follow-up

There were no treatment-related deaths on this study. Three Patients have died due to progression; one on the letrozole arm and two on the observation arm (see [Tables 1A and 1B](#)). One patient on the observation arm is alive with recurrent disease currently being treated. Five patients remain NED at last contact; three on the letrozole arm, and two on the observation arm. The study closed to accrual due to recommendations of the Data Safety Monitoring Board (DSMB) at MD Anderson Cancer Center. [Tables 2 and 3](#)

4. Discussion

No definitive conclusions can be made in this trial due to its low accrual. An attempt to rescue this trial through the NRG-Gynecologic Oncology Group was unsuccessful as it was determined standard chemotherapy and subsequently, intensive combination chemotherapy adjuvants were of higher priority. Early observations, however, are clinically thought provoking and deserve further investigation.

Aromatase inhibitors (AI) appear to have clinical activity against uterine leiomyosarcoma. The first prospective clinical trial of an AI in patients with metastatic uLMS examined the efficacy of using letrozole to treat patients with unresectable uLMS and with IHC-confirmed ER and/or PR expression. Letrozole achieved a 54% SD rate. Data suggested significant associations between patients with strong ER status and prolonged PFS ($p = 0.04$), and strong PR status and a prolonged PFS ($p = 0.01$). The median PFS, 12-week PFS rate, and 24-week PFS rate were 12 weeks, 50%, and 17% respectively. The longest PFS rates were achieved by patients whose tumors showed > 90% expression of ER and PR. ([George et al., 2014](#))

We are not certain as to why it was difficult to accrue to this trial. As we do not know the number of eligible patients treated at M.D. Anderson Cancer Center during this period, we are unable to state how many patients were missed to accrual. It is possible that the study did not attract many participants because letrozole was also available off study.

While this study was designed to be a practice-changing prospective trial, unfortunately it only accrued nine patients. Information obtained from this study can only be used in a hypothesis-generating way. Future trials, in addition to answering a compelling scientific/medical intervention will also need to address the feasibility/lack of accrual that we have seen in this trial. It is important that the gynecologic oncology and medical oncology communities, who treat these patients, come together to determine the best trial options. As discussed earlier, GOG-277 was closed to accrual after several years of being open. In that study, there were only 38 patients enrolled at 572 sites. ([Hensley et al., 2018](#))

Adjuvant therapy for patients with uLMS remains a high priority, and an unmet need. Even for patients with early stage disease, overall survival and progression-free survival are not ideal. While no definitive conclusions can be made, this study suggests that AI therapy in patients with early stage uLMS may be an active agent. Further investigation is warranted.

Authors' disclosures of potential conflicts of interest

A Randomized Phase II Study of Letrozole vs. Observation in Patients with Newly Diagnosed Uterine Leiomyosarcoma.

Brian M. Slomovitz: research support for Novartis.

Michael C. Taub: nothing to disclose.

Marilyn Huang: received a grant from Merck; consulting for Tesaro; received a grant from Janssen; consulting for Clovis.

Charles Levenback: nothing to disclose.

Robert L. Coleman: nothing to disclose.

Author contributions

Brian M. Slomovitz, MD: Corresponding author; Principal investigator; Wrote initial manuscript; Edited manuscript.

Michael Taub: Research assistant; Edited manuscript.

Marilyn Huang, MD: Edited manuscript.

Charles Levenback, MD: Patient accrual; Edited manuscript.

Robert L. Coleman, MD: Patient accrual; Manuscript preparation; Edited manuscript.

Acknowledgments

This study was financially supported by the Department of Gynecologic Oncology and Reproductive Medicine at the University of Texas M.D. Anderson Cancer Center.

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