References for Use of Aromatase Inhibitors in Uterine Leiomyosarcoma

Expression of ER and PR in up to 70–80% of uterine LMS has led to several studies examining the potential role of aromatase inhibitors (AIs).

The potential for favorable results with the use of AIs as a treatment has led to its inclusion as an option in NCCN guidelines for uterine sarcoma. See page from NCCN Guidelines for Patients, Uterine Cancer, inserted after page 2.

Two Phase II clinical trials involving the AI letrozole (Femara) have had findings published. The abstracts of the articles on these studies are attached on pages 4 and 5.

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

Brian M. Slomovitz, Michael C. Taub, Marilyn Huang, Charles Levenback, Robert L. Coleman

At MD Anderson, Houston 9 patients

February 2019, Gynecologic Oncology Reports

Phase 2 Trial of Aromatase Inhibition with Letrozole in Patients with Uterine Leiomyosarcomas Expressing Estrogen and/or Progesterone Receptors

Suzanne George, MD; Yang Feng, MS; Judith Manola, MS; Marisa R. Nucci, MD; James E. Butrynski, MD; Jeffrey A. Morgan, MD; Nikhil Ramaiya, MD; Richard Quek, MD; Richard T. Penson, MD; Andrew J. Wagner, MD, PhD; David Harmon, MD; George D. Demetri, MD; and Carolyn Krasner, MD

At Dana Farber, Boston 27 patients

March 2013, Cancer
Three retrospective studies discuss historical use of aromatase inhibitors in patients over several years at three institutions. Abstracts of the articles are appended as pages 6-8.

**Treatment of hormone positive uterine leiomyosarcoma with aromatase inhibitors**

Eirini Thanopoulou, Khin Thway, Komel Khabra and Ian Judson

At Royal Marsden Hospital, London, 16 patients

June 2014, Clinical Sarcoma Research

**Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors**

Roisin O'Cearbhaill, Qin Zhou, Alexia Iasonos, Robert A. Soslow, Mario. M. Leitao, Carol Aghajanian, Martee L. Hensley

At Memorial Sloan-Kettering, New York 40 patients

March 2010, Gynecologic Oncology

**Hormone receptor expression in uterine sarcomas: prognostic and therapeutic roles**


At Cedars-Sinai Medical Center, Los Angeles 40 patients

December 2009, Gynecologic Oncology
Guide 13. Low-grade ESS: treatment after surgery

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment after surgery</th>
</tr>
</thead>
</table>
| Stage 1 | **OPTION 1:** Surgery to remove the ovaries and fallopian tubes (preferred)  
**OPTION 2:** Watch-and-wait (no treatment) |
| • Stage 2  
• Stage 3  
• Stage 4A | Hormone therapy, with or without external beam radiation |
| Stage 4B | Hormone therapy, with or without radiation to help with symptoms |

Guide 14. UUS, uLMS, and high-grade ESS: treatment after surgery

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment options after surgery</th>
</tr>
</thead>
</table>
| Stage 1 | • Watch-and-wait (no treatment)  
• Systemic therapy |
| • Stage 2  
• Stage 3  
• Stage 4A | • Systemic therapy  
• External beam radiation therapy  
• Both of the above treatments |
| Stage 4B | • Systemic therapy (radiation therapy to help with symptoms may be added) |

Estrogen blockade if the tumor is estrogen receptor positive.

Options for treating stage II, III, and IVA uLMS, UUS, and high-grade ESS include:

- Systemic therapy
- EBRT

The main treatment after surgery for uLMS, UUS, and high-grade ESS that has metastasized (stage IVB) is systemic therapy. Palliative radiation therapy may be used to control symptoms or to prevent symptoms from occurring in the first place.
A randomized phase II study of letrozole vs. observation in patients with newly diagnosed uterine leiomyosarcoma (uLMS).

Slomovitz BM, Taub MC, Huang M, Levenback C, Coleman RL

Gynecologic Oncology Reports February 2019

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.

PMID
30519622

PMCID
PMC6260388
Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors


Cancer March 2014

Abstract

BACKGROUND:
Advanced uterine leiomyosarcoma (ULMS) is an incurable disease. A significant percentage of cases of ULMS express estrogen and/or progesterone receptors (ER and/or PR). To the authors’ knowledge, the role of estrogen suppression in disease management is not known.

METHODS:
The authors performed a single-arm phase 2 study of the aromatase inhibitor letrozole at a dose of 2.5 mg daily in patients with unresectable ULMS with ER and/or PR expression confirmed by immunohistochemistry. Tumor assessments were performed at baseline, 6 weeks, 12 weeks, and every 8 weeks thereafter. Toxicity was monitored throughout treatment. The primary endpoint was the progression-free survival at 12 weeks.

RESULTS:
A total of 27 patients was accrued, with a median of 2 prior treatment regimens (range, 0-9 treatment regimens). The median duration of protocol treatment was 2.2 months (range, 0.4 months-9.9 months). The 12-week progression-free survival rate was 50% (90% confidence interval, 30%-67%). The best response was stable disease in 14 patients (54%; 90% CI, 36%-71%). Three patients, all of whom had tumors expressing ER and PR in > 90% of tumor cells, continued to receive letrozole for > 24 weeks. The most common reason for treatment discontinuation was disease progression (85%). Letrozole was found to be well tolerated.

CONCLUSIONS:
Letrozole met protocol-defined criteria as an agent with activity in patients with advanced ULMS. Patients with the longest progression-free survival rate were those whose tumors strongly and diffusely expressed ER and PR.

© 2013 American Cancer Society.

PMID:
24222211
Treatment of hormone positive uterine leiomyosarcoma with aromatase inhibitors

Eirini Thanopoulou, Khin Thway, Komel Khabra, and Ian Judson

*Clinical Sarcoma Research*  June 2014,

**Abstract**

**Background**

Aromatase inhibitors (AIs) have not been used consistently as part of the management of hormone receptor positive uterine leiomyosarcomas (ULMS). As a result, the published data regarding the efficacy of AIs in this subtype of ULMS are sparse.

**Methods**

We performed a retrospective electronic medical record review of patients with ULMS treated with an AI, in the 1st or the 2nd line setting, at the Sarcoma Unit of the Royal Marsden Hospital between 2001 and 2012. We assessed progression-free survival (PFS), objective response and toxicities and explored the correlation of the intensity of the hormone receptor status, as well as of the grade with PFS.

**Results**

Sixteen patients with measurable advanced ULMS were treated with an AI in our unit. All of them were oestrogen receptor (ER) and progesterone receptor (PgR) positive. Letrozole was used in all patients as 1st line endocrine therapy, while exemestane was mainly prescribed as 2nd line (83%). Median PFS in 1st line was 14 months (95% CI: 0 – 30 months), and prolonged PFS was more likely to be observed in patients with low grade compared to high grade ULMS (20 months vs. 11 months), and in moderately/strongly ER positive compared to weakly ER positive ULMS (20 months vs. 12 months). Best response was partial response (PR) in 2/16 patients (12.5%) and clinical benefit (CB), defined as complete response (CR) + PR + stable disease ≥6 months, was observed in 10/16 patients (CB rate (CBR) 62.5%). Median duration of 2nd line was 3 months and median PFS was not reached. The 1-year progression-free rate for the 2nd line AI was 80%. Best response was PR in one patient and CBR was 50%. AIs were well tolerated in both lines of treatment.

**Conclusions**

In this population of patients with hormone positive ULMS, AIs achieved a significant CBR (62.5%) in 1st line, which was retained in 2nd line (CBR: 50%). The relatively prolonged median PFS (14 months), along with the favourable toxicity profile could place AIs among the first choices of systemic treatment in hormone positive ULMS, preferably in strongly positive (>90%), and/or low grade and low volume disease.
Treatment of advanced uterine leiomyosarcoma with aromatase inhibitors

Roisin O'Cearbhaill, Qin Zhou, Alexia Iasonos, Robert A. Soslow, Mario. M. Leitao, Carol Aghajanian, Martee L. Hensley

Gynecologic Oncology  March 2010

Abstract

BACKGROUND:
Aromatase inhibitors are sometimes used in the treatment of selected patients with uterine leiomyosarcoma (LMS), but there are few data assessing the efficacy of aromatase inhibitors in this setting.

METHODS:
We performed a retrospective electronic medical record review of patients with uterine LMS treated with an aromatase inhibitor at Memorial Sloan-Kettering Cancer Center between 1998 and 2008. We assessed progression-free survival (PFS) and objective response among patients with measurable disease and explored the correlation of hormone receptor status with outcome.

RESULTS:
Forty patients with advanced or recurrent uterine LMS were treated with aromatase inhibitors. Thirty-four patients had measurable disease. Hormone receptor status for these patients was as follows: estrogen receptor (ER) positive-22, ER negative-9, ER unknown-3, progesterone receptor (PR) positive-10, PR negative-10, PR unknown-14. Aromatase inhibitors used were letrozole (in 74% of patients), anastrozole (21%), and exemestane (6%). Median PFS was 2.9 months (95% CI: 1.8-5.1). The 1-year PFS rate was 28% (95% CI: 11-48%) for ER and/or PR positive uterine LMS. Best objective response was partial response (PR) in 3/34 patients (9%) (all of whom were ER positive).

CONCLUSIONS:
In this population of patients with mostly low-volume and ER positive uterine LMS, aromatase inhibitors achieved objective response in only 9%. Relatively prolonged PFS was observed among ER positive uterine LMS patients. In the absence of a no-treatment control group, the prolonged PFS cannot be attributed solely to the activity of the aromatase inhibitor treatment since it may reflect the underlying biology of low-volume, ER positive uterine LMS.

PMID: 19932916

PMCID: PMC4852374
**Hormone receptor expression in uterine sarcomas: prognostic and therapeutic roles**


*Gynecologic Oncology*  December 2009

**Abstract**

**OBJECTIVES:**
The utility of hormone therapy in the management of uterine sarcomas is poorly defined. We hypothesize that estrogen receptor (ER) expression is common in uterine sarcomas, and carries prognostic significance. Further, we hypothesize that ER-positive uterine sarcomas respond to hormone therapy.

**METHODS:**
We retrospectively reviewed charts of patients with uterine sarcomas. Stepwise Cox proportional hazards regression model was used to evaluate variables related to the risk of death: age, histology, stage, use of pelvic radiotherapy, and ER expression. In addition, we examined clinical outcomes in patients treated with aromatase inhibitors, megestrol acetate, depot medroxyprogesterone acetate, and tamoxifen.

**RESULTS:**
Fifty-four patients underwent immunohistochemical staining, and 34 (63%) were ER-positive. Kaplan-Meier survival analysis and log-rank test indicated that patients with ER-positive sarcomas demonstrated improved overall survival when compared with ER-negative patients (median OS 36 vs. 16 months, p=0.004). Upon multivariate analysis, ER positivity retained significance as an independent predictor of survival (HR=0.32, CI 0.12-0.89, p=0.03). Four patients received hormonal treatment in the adjuvant setting and remained in remission (range of follow up: 18-68 months). Eighteen patients received hormone therapy in the setting of recurrent or progressive disease: fourteen (78%) demonstrated stable disease or complete or partial response (range of follow up: 6-124 months).

**CONCLUSIONS:**
ER expression is common and is associated with improved overall survival in uterine sarcomas. Conducting immunohistochemical staining to ascertain ER status may aid with prognostication in this disease. Hormone therapy should be considered in patients with primary and recurrent ER-positive uterine sarcomas.

PMID: 19767065