Use of Aromatase Inhibitors as First- and Second-Line Medical Therapy in Patients With Endometrial Adenocarcinoma: A Retrospective Study

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Abstract

Objectives: The primary objective of this study was to examine the role of aromatase inhibitors (AIs) as first- or second-line medical treatment in women with endometrial adenocarcinoma who were not candidates for surgical management. The secondary objective was to examine the role of AIs in adjuvant and palliative treatment. Methods: Thirty women with endometrial adenocarcinoma who were treated with aromatase inhibitors between 2000 and 2010 at the Tom Baker Cancer Centre in Calgary, Alberta were assessed in a retrospective analysis. Disease response was based on response evaluation criteria in solid tumours. Kruskal-Wallis test was used to compare non-parametric variables and Fisher exact test was used to compare the health variables.

Results: Seventeen patients received AIs as first- or second-line medical treatment, five received adjuvant therapy, and eight received palliative treatment. The median age of patients in the first or second line medical treatment group was significantly greater than that of patients in the adjuvant or palliative group (P = 0.042). There was no significant difference in median weight or body mass index. The subjective clinical response rate with medical treatment was 70%. In the first- or second-line medical treatment group, only seven patients had available response data. Our study showed stable disease in 5/7 (71%), partial response in 1/7 (14%), and progression in 1/7 (14%) patients.

Conclusion: This retrospective clinical series examining use of an aromatase inhibitor as first- or second-line medical therapy in women with endometrial carcinoma showed that AIs are a potential treatment for patients who have a contraindication to surgery and who either have failed or cannot use megestrol therapy.

Résumé

Objectifs : L’objectif principal de cette étude était d’examiner le rôle des inhibiteurs de l’aromatase (IA) à titre de traitement médical de première ou de deuxième intention chez des femmes présentant un adénocarcinome endométrial qui n’étaient pas candidates à la prise en charge chirurgicale. Son objectif secondaire était d’examiner le rôle des IA dans les traitements adjuvants et palliatifs.

Méthodes : Trente femmes présentant un adénocarcinome endométrial qui ont été traitées au moyen d’inhibiteurs de l’aromatase entre 2000 et 2010 au Tom Baker Cancer Centre de Calgary, en Alberta, ont fait l’objet d’une analyse dans le cadre d’une analyse rétrospective. La réaction de la maladie a été fondée sur les critères d’évaluation de la réaction dans le cas des tumeurs solides. Le test de Kruskal-Wallis a été utilisé pour comparer les variables non paramétriques et le test exact de Fisher a été utilisé pour comparer les variables de santé.

Résultats : Dix-sept patientes ont reçu des IA à titre de traitement médical de première ou de deuxième intention, cinq autres ont reçu un traitement adjuvant et les huit dernières ont reçu un traitement palliatif. L’âge médian des patientes du groupe « traitement médical de première ou de deuxième intention » était considérablement plus avancé que celui des patientes des groupes « adjuvant » ou « palliatif » (P = 0.042). Aucune différence significative n’a été constatée en matière de poids médian ou d’indice de masse corporelle. Le taux subjectif de réaction clinique était de 70 % dans le cas du traitement médical. Pour ce qui est du groupe « traitement médical de première ou de deuxième intention », nous ne disposions de données sur la réaction que pour sept patientes. Notre étude a indiqué une
well-differentiated disease, with no myometrial invasion or treatment has been suggested for women with early stage, a five-year survival of 75% to 85%.1,2 Twenty-five percent agonists,7,8 and these are used only when progestogen tamoxifen with or without gonadotropin-releasing hormone line medical treatments for primary therapy have included dose progestins.7 for progestogen therapy because of side effects of high- not only poor surgical candidates but also poor candidates (e.g., with gross obesity or medical disorders).2,4 women in whom this approach is used include those who carcinoma. Rarely, medical therapy may be considered; cornerstone of treatment for women with endometrial Surgery, specifically hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy, is the cornerstone of treatment for women with endometrial carcinoma. Rarely, medical therapy may be considered; women in whom this approach is used include those who wish to preserve fertility and those who are not good surgical candidates (e.g., with gross obesity or medical disorders).2,4 First-line medical therapy has usually consisted of oral progestogens, with response rates of 30% to 75%.2,5–8 This treatment has been suggested for women with early stage, well-differentiated disease, with no myometrial invasion or intra-abdominal spread.2 Close monitoring for all patients with primary medical treatment is essential to detect recurrence or extension into extraterine tissues.7 Second- line medical treatments for primary therapy have included tamoxifen with or without gonadotropin-releasing hormone agonists,7,8 and these are used only when progestogen therapy fails. Severely obese patients (BMI > 45 kg/m²) are not only poor surgical candidates but also poor candidates for progestogen therapy because of side effects of high- dose progestins.7

Another possible medical treatment option includes the use of aromatase inhibitors (AIs). AIs interfere with the function of the enzyme aromatase, suppressing the conversion of testosterone to estrogen9,10 by up to 90% to 98%.9,11 This effect is overcome in premenopausal women by an up-regulation of follicle-stimulating hormone.9 Patients on AIs have fewer hot flashes and less vaginal bleeding, but higher risk of myalgia, arthralgia, osteoporosis, and fractures than patients taking tamoxifen.9 However, they also have less weight gain than patients taking megestrol acetate,7,12,13 with no difference in the likelihood of developing edema, thromboembolism, gastrointestinal symptoms, hot flashes, or vaginal dryness.13 Previous thromboembolism and thrombophilia, however, are indications for caution with progestogen use.14,15

The largest studies of AIs in women with endometrial cancer have been performed in those with advanced or recurrent disease, with response rates of approximately 9%.13,16 Only three studies have been performed using AIs for first- or second-line medical therapy. These studies used endometrial thickness as a surrogate marker for disease response. All three studies found a decrease in endometrial thickness of 40% to 67%,10,17,18 but none commented on survival or response rates. Treatment with AIs may therefore be a viable option in treating endometrial cancer, but patients must be chosen carefully for appropriate prognostic factors, including tumour grade, cell type, age, stage, and performance status.1,4,13

The benefits of AIs for first- or second-line medical therapy in patients with endometrial carcinoma remain unclear. To clarify this issue, we performed a retrospective study of patients with endometrial carcinoma treated with AIs at the Tom Baker Cancer Centre between 2000 and 2010. We hypothesized that aromatase inhibitors have a role in the medical management of low-grade, early-stage endometrial carcinoma.

**METHODS**

We performed a retrospective chart review of women with endometrial carcinoma treated with AIs between 2000 and 2010 at the Tom Baker Cancer Centre in Calgary, Alberta. Charts were extracted from the cancer centre’s electronic medical record (the ARIA oncology information system). Any missing information was followed up by examining all paper records available. The inclusion criteria for the study were being an adult woman (> 18 years old) with endometrial cancer treated with an AI. We excluded women with a diagnosis other than endometrial adenocarcinoma (e.g., sarcoma) and those whose primary site of disease was unknown. All women deemed eligible for the study were included. An a priori study size was not determined because all eligible patients were included.
Our primary research question was “In women with endometrial cancer who are not surgical candidates, can aromatase inhibitors be used for first- or second-line medical treatment?” The primary outcome of this study was response rates of patients with endometrial endometrioid adenocarcinoma who were treated with AIs. The secondary outcomes were overall survival rates and duration of AI use.

Responses were determined on the basis of response evaluation criteria in solid tumours (RECIST), when available. Lesions were classified as progressive disease, stable disease, or partial or complete response on the basis of available biopsy results (curettage or hysterectomy specimens), diagnostic imaging results, or clinical symptoms. Overall survival was defined as the interval from the date of initial diagnosis to the date of death or date of last known contact. Duration of treatment was defined as the interval from the date of initial diagnosis to the date of death or date of last known contact. Duration of treatment was defined as the interval from the date of initiation of AI to the date of discontinuation, death, or last contact. No distinction was made between cancer-related and non-cancer-related deaths. Data were also collected on patients’ age, stage and grade of disease, weight, height, body mass index, surgery, and tumour histology.

This study was a retrospective review based on acquired data, and did not interfere in any way with the care that the women received. Subjects were not contacted directly. Individual informed consent was therefore not required.

We used SPSS version 15.0 (IBM Corp., Armonk, NY) for statistical analysis. A Kruskal-Wallis test was used to compare non-parametric variables in the three treatment groups (first- or second-line medical, adjuvant, and palliative), specifically comparing median age, weight, and BMI. Fisher exact test was used to compare the health variables between the three treatment groups. If data were missing, all paper and available electronic records were reviewed. If the data were still unavailable, the patient was not included in the final analysis.

Research ethics committee approval was provided by Alberta Cancer Research Ethics Board.

RESULTS

A total of 180 patients with endometrial adenocarcinoma were treated with a hormone therapy between 2000 and 2010. One hundred seventy patients were treated with megestrol acetate, two with goserelin, and 30 with an AI.

Of the 30 patients who received an AI, 17 had first- or second-line medical treatment (i.e., without previous surgery or radiation therapy), five had adjuvant treatment.
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(i.e., after primary treatment with surgery or radiation), and eight had palliative treatment (Table 1). In the first- or second-line medical treatment group, 16 of 17 were given anastrozole and one received letrozole. In the adjuvant and palliative groups, only one patient in each group received letrozole; four of five in the adjuvant group and seven of eight in the palliative group received anastrozole. Side effects in all groups were mild, and the medications were well tolerated. Only eight of the 30 treated patients reported any side effects; these included dry cough, abdominal cramps, dyspnea, edema, wheezing, hot flashes, headache, fatigue, arthralgia, hair thinning, nausea, decreased appetite, and weight loss. Within the first- or second-line medical therapy group, only three of 17 patients had side effects: one had dry cough, one had abdominal cramps, and one had swelling, dyspnea, and edema.

In the first- or second-line medical therapy group, no patients had had prior surgery or radiation therapy. Megestrol acetate was given to 10 of 17 patients (59%) prior to AI use, and three of 17 (18%) received megestrol after completion of AI therapy. Of the patients who received prior megestrol, three switched to an AI because of unacceptable side effects, four because of a thrombotic event (pulmonary embolism or deep vein thrombosis), and three more because of persistent clinical symptoms or proven progressive disease. Four patients received radiation therapy after treatment with an AI because of persistent disease or a return of clinical symptoms, and one patient received chemotherapy (Figure 1). The average age of patients in this group was 73 years (range 34 to 95 years), with a median age of 84. The average weight was 101 kg (median 84 kg) and the average BMI was 42 kg/m² (range 16.3 to 78.1 kg/m²; median 35.2 kg/m²) (Table 1). Many of these patients had multiple medical conditions or a grossly elevated BMI that served as a contraindication to surgery or progestogen therapy. One patient declined surgery in order to preserve fertility.
The median age of patients in the first- or second-line medical treatment group was significantly greater than patients in the adjuvant and palliative groups ($P = 0.042$).

In the adjuvant therapy group, four of five patients had a primary hysterectomy and bilateral salpingo-oophorectomy, three of five patients had bilateral pelvic lymphadenectomy, and one patient had primary radiation therapy (Table 2). Megestrol was given to two of five patients (40%), and chemotherapy was used in three of five patients (60%) prior to AI use. One of the five patients began on AI therapy because of side effects from megestrol acetate, another began AI therapy as a prophylactic adjuvant, two began an AI because of breast cancer, and one began AI therapy for an unknown reason. The palliative care group had similar results to the adjuvant group, with all eight patients having a hysterectomy, seven of eight having bilateral salpingo-oophorectomy, and four of eight having bilateral pelvic lymphadenectomy. Six of eight patients (75%) were treated with adjuvant megestrol and five of eight (63%) were treated with adjuvant chemotherapy. The average age of patients in the adjuvant group was 54 years (range 48 to 63 years; median 52 years) and in the palliative group it was 57 years (range 44 to 70 years; median 55.5 years) (Table 1). The average weight of patients in the adjuvant group was 113 kg, with a mean BMI of 42 kg/m² (range 27.6 to 53.7 kg/m²); in the palliative group the average weight was 87 kg with a mean BMI of 32 kg/m² (range 21 to 51.6 kg/m²). Patients in the adjuvant treatment group were more likely to have had breast cancer ($P = 0.02$). There was no significant difference between groups for any other measured health variables, and no difference in BMI or weight between the three treatment groups (Table 1).

Because of the poor medical condition and increased age of the patients treated with medical AI therapy, very few biopsies and diagnostic tests were available for review. Of the 17 patients in this group, six had follow-up biopsies and only four had follow-up imaging. One of the six biopsies (17%) showed a response to therapy, four (67%) showed persistent cancer, and one (17%) continued to show no evidence of cancer. On subsequent diagnostic imaging, three of four (75%) had stable disease and one had progressive disease. Combining patients who had biopsies and diagnostic imaging, one patient out of seven (14%) showed a response to therapy, one (14%) had progressive disease, and five of seven (71%) had either stable disease or no response (i.e., persistent cancer on biopsy) (Figure 2). Only one of 17 patients had any documented disease outside the pelvis (retroperitoneal lymph nodes seen on CT scan). Ten of the 17 patients were followed only clinically, and seven of those 10 had a clinical response to treatment with subjective improvement in bleeding, feelings of pressure, and discomfort. Eight of 17 patients continued using an AI until the date of death. Three of 17 discontinued the medication because of progressive or persistent disease, and three discontinued for unknown reasons. None of the patients with documented side effects stopped the medication for this reason. Three patients with an initial improvement in clinical symptoms discontinued the medication because of a recurrence of symptoms, with a mean duration of response of 41.1 weeks (range 23 to 62.6 weeks).

In the adjuvant therapy group, a clinical response was seen in one patient, and follow-up diagnostic imaging showed no visible disease in three patients. Because of poor prognoses and patient preferences in the palliative group, biopsies and diagnostic imaging tests were rarely undertaken, and therefore relevant data were limited. Biopsy results were available for two of eight patients and diagnostic imaging results were available for five of eight patients. Combined results revealed two of five patients (40%) with stable disease, two of five (40%) with progressive disease, and one of five (20%) with a partial response (Figure 2). The single patient with a partial response also had clinical improvement in symptoms. Within the palliative care group, three of eight patients had no reason recorded for discontinuation of the medication, two had progressive disease, one had unacceptable side effects, and two of eight continued on the medication until the date of last contact. The mean overall survival in the adjuvant therapy group was 339 weeks.
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weeks and in the palliative care group was 448 weeks. The average duration of AI use was 116 weeks in the adjuvant group and 69 weeks in the palliative group (Table 2).

**DISCUSSION**

The primary objective of our study was to determine whether aromatase inhibitors could be used as first- or second-line medical management in women with endometrial carcinoma who were not candidates for surgical management. We found a partial response in one of seven patients (14%) and stable disease in five of seven (71%). The subjective clinical response seen in patients was 70%, suggesting a role for AI therapy in patients who are not fit for surgery. Our study acts as a preliminary analysis of this question, and serves as a starting point for further prospective trials.

Aromatase inhibitors, by interfering with aromatase, an enzyme responsible for the conversion of testosterone into estrogen,9,10 cause a 95% to 98% reduction in circulating estrogen levels.11 These third generation aromatase inhibitors are grouped into steroidal (exemestane) and nonsteroidal (anastrozole and letrozole) categories.2,8,9 The nonsteroidal aromatase inhibitors bind reversibly to the heme moiety of the cytochrome P450 enzyme and therefore must be given on a regular basis, in contrast to steroidal aromatase inhibitors, which bind irreversibly to the catalytic site of the enzyme.2,8,9,11 In the treatment of breast cancer, aromatase inhibitors are found to be most effective in postmenopausal women because of the relative inactivity of the hypothalamic-pituitary-ovarian axis; there is little estrogen production in the ovaries, with the majority of estrogen being produced in the adrenal glands and peripheral adipose tissue.2,9,10,12,13 Hence, aromatase inhibitors have become the standard of care for the treatment of breast cancer in postmenopausal women.9,12

Aromatase inhibitors have also been used in premenopausal women for infertility treatment. Several studies have shown that short term use of letrozole results in ovarian stimulation by increasing levels of
follicle-stimulating hormone. Prolonged use of AIs will result in an initial proliferation of ovarian follicles, followed by subsequent inhibition of the menstrual cycle, with no known long-term effect on fertility. Because of the initial ovarian stimulation, it is crucial for premenopausal women to use an effective form of contraception while on this medication.

Aromatase production is elevated in endometrial cancer stroma, with up to 66.7% of cancers expressing the enzyme. Endometrial cancers have increased in situ aromatase activity, in both estrogen-receptor–positive and estrogen-receptor–negative tumours, when compared with normal endometrium. Locally produced estrogen may act in a paracrine fashion and further stimulate cancer growth. In some studies, aromatase activity appears to decrease in more advanced disease, whereas others have found no correlation between tumour grade or stage and aromatase expression. On the basis of these biochemical trials, it was felt that use of an AI might have a role in endometrial cancer therapy.

Several small studies have investigated the role of AIs in recurrent or palliative endometrial cancer. Rose et al. enrolled 23 patients with recurrent endometrial cancer and treated them with anastrozole 1 mg/day for a minimum of 28 days. Partial response was seen in two patients (9%), with a median progression-free survival of one month and an overall survival rate of six months. A weakness of this study was a selection bias towards high grade cancers, with nine of the 23 patients having grade 2 carcinoma and 14 of 23 having grade 3 carcinoma. Ma et al. performed a multicentre phase 2 study with the National Cancer Institute of Canada in 32 women with recurrent endometrial cancer. Patients were treated with letrozole 2.5 mg daily and had an overall response rate of 9.4%. Bellone et al. reported a case of chemotherapy-resistant endometrial cancer that responded to treatment with anastrozole. Our study, unlike that of Rose et al., had a higher proportion of low grade recurrent tumours, with five of seven patients having grade 1 carcinoma and two of seven having grade 2 (Table 2). Even with these lower grade tumours, the response rate to AIs remains low, with only one patient achieving a partial response. All available data on grading of tumours are shown in Table 2. The overall survival in our first- or second-line medical treatment group was 35 months, which was longer than the reported overall survival rate of six months in the report of Rose et al. Our response rate in the palliative or recurrent setting is in agreement with the other published studies and suggests a low rate of effectiveness. On the other hand, all eight of our palliative patients had undergone surgery, six had undergone treatment with megestrol acetate, and seven had undergone chemotherapy over the course of their disease, leaving very limited options for further treatment. It would therefore be feasible to consider using an AI in a patient with a grade 1 or 2 endometrial adenocarcinoma when all other options have been exhausted or are contraindicated.

Medical treatment of endometrial cancer with AIs is a relatively recent development. Burnett et al. reported two cases of endometrial carcinoma treated with a combination of medroxyprogesterone acetate and anastrozole; the women in both of these cases responded to primary therapy. Bershtein et al. studied the effect of anastrozole as neoadjuvant therapy for endometrial cancer and demonstrated a decrease in endometrial thickness of 40% to 60%. These authors also found a decrease in intra-tumour aromatase activity and serum estradiol levels. Barker et al. confirmed these findings in a retrospective study of 16 patients with endometrial hyperplasia and carcinoma. The mean endometrial thickness on ultrasound decreased by 67.1% in patients with endometrial carcinoma. Finally, Garuti et al. performed a prospective study in 45 patients receiving AIs for breast cancer. They found that the endometrial thickness in these patients decreased by 59% to 64% after 36 to 48 months of AI therapy.

Our study represents one of the first retrospective reviews of AI use and outcomes in the clinical setting. In the adjuvant setting, there appears to be a low response rate. The retrospective nature of our trial limited our ability to examine the indications for adjuvant AI use, as noted above. Given that the outcomes in our adjuvant group were not directly compared with those of a “non-treatment” group, we feel that there is no role for AI use in the adjuvant setting until further research has been conducted. Our study population represents a unique and small group of individuals. Many were elderly women, with a mean age of 73 years. Many also had concurrent medical conditions that were deemed to contraindicate megestrol therapy (e.g., pulmonary embolism or deep vein thrombosis in 35%) or surgery (e.g., myocardial infarction or angina in 29%, stroke in 18%, congestive heart failure in 35%, and pulmonary hypertension in 12%) (Table 1). There was no significant difference in concurrent medical conditions between the three groups, although the lack of significance was likely due to small sample size. Women with adjuvant therapy were more likely to have had breast cancer than those treated medically or palliatively (P = 0.02). Finally, the women in our first- or second-line medical therapy and adjuvant care group
had a high mean BMI (42 kg/m²; range 16.3 to 78.1 kg/m²), often making surgery difficult or contraindicated. However, there was no difference in either BMI or weight between our three treatment groups (Table 1). This suggests that our centre does not select patients for primary medical treatment based on weight alone. As noted, 14 of 17 patients in our first- or second-line medical group still received megestrol at some point during their therapy.

This study has several limitations. First, it was a retrospective review with a small number of patients. The specific selection criteria we used created a selected population for retrospective review. Second, follow-up information was lacking in several cases. In our first- or second-line medical treatment group, 10 of 17 patients were over the age of 80. These women had other contraindications to surgery and were therefore given primary medical management. Many of these women did not consent to further biopsy or imaging because these measures would not change their management. Endometrial cancer is a relatively slow growing neoplasm, and the likelihood of this disease causing death was low. Further information on the specific cause of death in each case would have been very useful, but was unavailable from the database. Although our response rate in the medical treatment group could be assessed in only seven patients, a clinical response was noted in seven of 10 patients. Third, a quality of life assessment is a crucial component of any study on AI use in women with endometrial cancer. We were unable to collect this information from the chart review. Retrospectively distinguishing side effects of AI use from symptoms of cancer or other systemic illnesses is difficult. We attempted to overcome this by noting any side effects or symptoms that appeared to occur at the time of AI use or to dissipate after AI discontinuation.

Further studies are necessary to determine the full effects of AI treatment on endometrial carcinoma, with specific focus on quality of life indicators and AI side effect profiles. A prospective study in a group of women who are unfit for surgery is needed, but this would require a multicentre trial because of the limited number of such women in any single centre. Another possible therapeutic approach that should be investigated in this group of women is a combination of AI with megestrol or AI with a levonorgestrel intrauterine system for the primary treatment of low-grade, early-stage endometrial endometrioid adenocarcinoma.

CONCLUSION

In this retrospective study of AI use in women with endometrial carcinoma, 70% had improvement in symptoms with first- or second-line medical treatment. Therefore, AIs may have a potential role in the treatment of patients who have a contraindication to surgery, who have failed megestrol therapy, or who cannot use a progestogen-based therapy. Further study is necessary to fully elucidate the true effects of AIs in women with endometrial carcinoma.

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REFERENCES


