Phase 2 study of anastrozole in recurrent estrogen (ER) / progesterone (PR) positive endometrial cancer: The PARAGON trial – ANZGOG 0903

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Abstract

Background: The clinical benefit rate with AI's and the impact of treatment on quality of life (QOL) in endometrial cancer is unclear. We report the results of a phase 2 trial of anastrozole in the endometrial cancer subgroup.

Methods: Investigator initiated single-arm, open label trial of anastrozole, 1 mg/d in patients with ER and /or PR positive hormonal therapy naive metastatic endometrial cancer. Patients were treated until progressive disease (PD) or unacceptable toxicity. The primary end-point was clinical benefit (response + stable disease) at 3 months. Secondary endpoints include progression-free survival (PFS), quality of life (QOL) and toxicity.

Results: Clinical benefit rate in 82 evaluable patients at 3 months was 44% (95% CI: 34-55%) with a best response by RECIST being partial response in 6 pts (7%; 95% CI: 3-15%). The median PFS was 3.2 months (95% CI: 2.8-5.4). Median duration of clinical benefit was 5.6 months (95% CI: 3.0-13.7). Treatment was well tolerated. Patients who had clinical benefit at 3 months reported clinically significant improvements in several QOL domains compared to those with PD, which was evident by 2 months including: emotional functioning (39 vs 6%: p = 0.002), cognitive functioning (45 vs 19%: p = 0.021), fatigue (47 vs 19%: p = 0.015) and global health status (42 vs 9%: p = 0.003).

Conclusion: Although the objective response rate to anastrozole was relatively low**,** clinical benefit was observed in 44% of patients with ER/PR positive metastatic endometrial cancer and associated with an improvement in QOL.

Introduction

The incidence of endometrial cancer is rising and in developed countries it is now the commonest gynaecological malignancy[1]. Although many patients are cured with surgery alone there remains a proportion who will relapse despite surgery and adjuvant therapy. Treatment of patients with relapsed or metastatic disease is challenging as standard cytotoxic chemotherapy infrequently results in prolonged disease control and can be associated with significant toxicity in a population who are often elderly and have other significant co morbidities.

Estrogen, plays a key role in the pathogenesis of endometrial hyperplasia and endometrioid adenocarcinoma type I. Most of these Type 1 endometrioid carcinomas are associated with endometrial hyperplasia and are also ER/PR positive, p53 negative and have a low Ki-67. There is evidence that hormonal therapy can be associated with clinical benefit in patients with recurrent/metastatic EC and is widely used to treat a subset of patients. Most work to date has focussed on the role of progestogens and historically response rates of up to 70% were reported in women with PR-positive endometrial cancers compared with 12% in women with PR-negative tumors [2-4]. However, using more rigorous response criteria in clinical trials and institutional studies, the objective response rates are much lower and range from 15% to 20% [2]. Medroxyprogesterone is approved by the FDA for the treatment of women with

97 EC but can be associated with significant adverse effects, including weight gain,
98 hypertension, fluid retention, increased blood sugar, insomnia, tremor,
99 thrombosis, and pulmonary emboli. These can potentially worsen quality of life
100 and may be life threatening [2]. There has been interest in the potential role of
101 aromatase inhibitors in EC given their activity in ER positive breast cancer and
102 superiority to tamoxifen in breast cancer. In addition, aromatase is highly
103 expressed in the endometrial stroma, and is responsible for local synthesis of
104 estrogens which may promotes estrogen-induced proliferation of tumour cells.
105 The reported response rates to aromatase inhibitors in recurrent and metastatic
106 endometrial cancer have generally been low. To date 6 studies have reported the
107 use of aromatase inhibitor therapy in advanced or recurrent endometrial cancer
108 [5-10] including a total of 104 patients. Response rates vary but are in the order
109 of 10% [11], and this almost certainly reflects the population who were treated
110 [6]. In the studies that have been reported, most patients have had high-grade,
111 hormone receptor-negative cancers, where a low likelihood of response would
112 be expected. There is still a need to evaluate aromatase inhibitors in women with
113 well-differentiated and/or hormone receptor-positive tumors, where the
114 expected response to an aromatase inhibitor is likely to be higher, as well as to
115 evaluate the impact of treatment on quality of life.
116 The Paragon (ANZGOG-0903) trial is an investigator-initiated basket trial
117 investigating the activity of anastrozole in post-menopausal patients with a wide
118 range of ER or PR positive recurrent or metastatic gynaecological tumours. It
119 includes 7 separate phase 2 open label prospective trials in different
120 gynaecological cancer types embedded within the one protocol. Here we report
121 the results of the prospective trial in the endometrial cancer cohort which aimed

to investigate the clinical benefit rate of the use of anastrozole, an aromatase inhibitor, in women with hormone receptor positive recurrent or metastatic endometrial cancer with an additional focus on the impact on quality of life.

Materials and Methods

The study design was a single-arm, open label trial of anastrozole at a dose of 1mg daily in post-menopausal women with ER and/or PR positive hormone naïve recurrent endometrial cancer. Patients were treated until disease progression by RECIST version 1.1 criteria or unacceptable toxicity.

Eligibility

Eligible patients had recurrent or metastatic endometrial cancer that was ER and/or PR positive. ER and/or PR positivity was defined as at least 10% of cells staining positive for ER and/or PR in their primary tumour or a biopsy of recurrent disease. In addition, eligible patients were postmenopausal, had no prior anti-cancer endocrine treatment, aged ≥ 18, ECOG performance status 0 – 2, had a life expectancy of >3 months, and measurable disease by RECIST v 1.1 criteria. Women receiving hormone replacement therapy or those with significant hepatic (bilirubin >2x upper limit of normal) or renal dysfunction (creatinine >3x upper limit of normal) were excluded. The baseline evaluation included history, physical examination, ECOG performance status, abdominal and pelvic computed tomography (CT) scan, full blood count, blood chemistry and liver function tests.

Study objectives

The primary objective was to assess the clinical benefit rate, defined as the proportion of patients who had response or stable disease at 3 months by RECIST 1.1 criteria. Secondary objectives included progression free survival (PFS), response duration, quality of life, and toxicity. Quality of life (QOL) and tolerability was assessed using the EORTC QLQ-C30 and the FACT-ES subscale score. The proportion of patients experiencing grade 3 or 4 toxicities as well as number of patients who came off therapy because of adverse events were also documented. The QLQ-C30 is the core module of the EORTC's quality of life questionnaire (QLQ) suite [12] and contains 5 functional scales (physical, role, emotional, cognitive and social functioning), overall health/global HRQL (global health status (GHS)), and 9 symptom/difficulties scales. Definitions for minimal important difference (MID) were adopted from Cocks et al 2011 for the EORTC QLQ-C30 [13]. Subjective endocrine-related symptoms were assessed by Functional Assessment of Cancer Therapy - Endocrine Symptoms (FACT-ES) subscale, a validated 5-point response scale developed for breast cancer research [14].

Response and Toxicity Assessment

Response status was assessed using RECIST v1.1 criteria. Clinical deterioration in the absence of proven progression was determined by the treating physician. CT scans were done at baseline and repeated every 3 months while patients remained on the trial. Adverse events were collected monthly for the first 3 months and then 3 monthly and toxicity was graded according to NCI CTCAE

V4.0. Quality of life was measured at registration prior to commencing anastrazole, monthly for the first 3 months, and 3 monthly thereafter until progression.

Statistical considerations

The expected clinical benefit rate at 3 months in the endometrial cancer cohort was 20% based on a literature review. To provide sufficient precision in the estimates of clinical benefit, a sample size of 75 patients was planned. The study had a stopping rule to allow for termination if there was lack of efficacy. There was a pre-planned interim analysis after 25 evaluable subjects had been on study for at least 3 months (and received at least 2 weeks of treatment). The data were reviewed by an Independent Data Monitoring and Safety Committee who recommended continued recruitment to 75 patients since the minimum number of responses required to be consistent with the expected clinical benefit rate was observed (i.e., at least 2).

Analysis of the efficacy (overall RECIST response/clinical benefit) was performed using the proportion of patients who responded/experience clinical benefit together with 95% confidence interval for the estimates. These rates were based on all patients receiving anastrozole for the first 2 weeks (intention to treat population) as well as patients who were on study for at least 4 weeks (evaluable for response). Toxicity analysis was evaluated by treatment received. Comparisons were 2-tailed and a nominal significance level of 0.05 was applied. Progression-free survival and duration of clinical benefit were analyzed using time-to-event methods, with Kaplan-Meier survival curves constructed for graphical display and unadjusted log-rank tests performed where appropriate.

Death from any cause was considered an event. 95% CIs for proportions were constructed using the modified Wilson method [15]. The conditional binomial exact test was used to test for association between binary variables. The paired t-test was used to compare baseline and on study QoL scores at individual time-points. In addition, change scores between baseline and on-study averaged scores were also computed and assessed using one-sample t tests. The proportion of pts whose score improved by ≥10-points (considered clinically relevant) was calculated for each QLQ-C30 subscale. Linear regression was used to compare change in QoL scores between patients achieving a 3-month clinical benefit and those who progressed, with adjustment for the baseline score.

PARAGON is a Gynaecologic Cancer InterGroup trial led by the Australian New Zealand Gynecological Oncology Group (ANZGOG) and coordinated by the NHMRC Clinical Trials Centre, University of Sydney. The collaborating groups are Cancer Research UK and the Belgian Gynaecological Oncology Group. The Study was performed in accordance to the NHMRC Statement on Ethical Conduct in Research Involving Humans and the Declaration of Helsinki. Ethical approval was obtained at all participating sites and all participants provided signed, written, informed consent.

PARAGON is registered on the Australian New Zealand Clinical Trials Registry (#ACTRN12610000796088)

Results

84 eligible patients with ER and/or PR positive recurrent or metastatic endometrial cancer were enrolled in 31 centres in Australia (n = 40), the UK (n = 38), New Zealand (n = 2) and Belgium (n = 4) between Feb 2012 and March 2014 (Consort diagram, figure 1). Mean age was 68 years (range 36-89). 50% patients had received prior chemotherapy whilst 67% had received prior radiotherapy, table 1.

There was a wide distribution of initial stage and grade of tumours with 24 (29%) tumours reported as grade 3 and 50 (60%) >= FIGO stage 2 at diagnosis. One patient withdrew before taking any study drug whilst one further patient took drug for less than 1 week leaving 82 patients eligible for analysis. All eligible patients received anastrozole 1mg daily until clinical progression, figure 1.

Clinical Response

Clinical benefit at 3 months was recorded in 36/82 patients (44%; 95% CI: 34-55%). A best RECIST response of partial response was observed in 6 patients (7%; 95% CI: 3-15%). The median PFS for the whole cohort was 3.2 months (95% CI: 2.8 – 5.4), figure 2a, with PFS being superior in patients with a treatment free interval prior to registration of greater than 12 months, figure 2b. The median duration of clinical benefit was 5.6 months (95% CI: 3.0 – 13.7), figure 2C. Fifteen patients remained on treatment for over a year. Partial responses were seen only in patients with grade 1 or 2 EC, but prolonged disease control was observed in 2 patients with grade 3 EC (figure 3).

Safety

Toxicity data were available for 82 of the 83 patients who received treatment. In general, treatment was well tolerated with the toxicity profile being as expected for an aromatase inhibitor. The commonest side effects were hot flushes (44%), arthralgia (48%) and fatigue (69%). The 7(9%) grade 3 toxicities were confined to fatigue, which could be related to treatment or disease. There were no grade 4 toxicities (table 2) and no patient stopped treatment due to adverse events. Other adverse events reported during treatment were considered disease-related and included abdominal ascites, abdominal distension, small intestinal obstruction, cellulitis, abdominal pain, small intestine fistula, pulmonary embolus and pneumonia.

QoL

QOL data was available for 79 of the 84 registered patients; Belgium did not participate (n=4) in the QoL component of PARAGON. Compliance with completing QoL questionnaires was high: 95% completed QoL questionnaires at baseline (76/80 patients), 93% at 1 month (70/75), 96% at 2 months (67/70) and 95% at 3 months (53/56); 71 completed QoL at both baseline and follow-up.

For the total cohort there were no statistically significant changes from baseline in the QLQ-C30 subscales averaged over the total time on-study. By time-point, emotional functioning scores improved significantly albeit by a small amount at months 1 and 2 i.e., (n = 67; mean change: 3.2 points; 95% CI: 0.3-6.1; p = 0.03)

and (n = 65; 4.7; 95% CI: 1.0-8.4; p = 0.02) respectively. For those still on study at 6-months (n = 31), scores improved significantly for cognitive functioning (8.1; 95% CI: 1.4-14.7; p = 0.02) and diarrhoea (-8.6; 95% CI: -15.6- -1.6; p = 0.02); these changes are defined as small (subtle but clinically relevant) and medium respectively by Cocks et al[13]. At 3-months (n=51) nausea and vomiting worsened significantly by a small but significant amount (4.9; 95% CI: 0.6-9.2; p=0.03).

No significant changes from baseline in FACT-ES total scores (range 0-180) were seen at any time point or averaged over the total on-study period. For the emotional well-being subscale (range 0-24) scores improved significantly by 1.1 points averaged over the total time on study (95% CI: 0.32-1.82; p = 0.006). FACT-G (range 0-108) scores improved significantly at 6-months by 3.8 points on average (n = 29; 95% CI: 0.1-7.5; p = 0.05).

In analyses stratified by 3-month clinical benefit status, patients recorded as having a clinical benefit were more likely to report clinically significant improvements of at least 10 points in several QoL domains after the first 2 months of treatment including improvements in: emotional functioning (39 vs 6%: p = 0.002), cognitive functioning (45 vs 19%: p = 0.021), fatigue (47 vs 19%, p = 0.015) and global health status (42 vs 9%: p = 0.003). In addition, the difference in averaged on-study changes for months 1-3 significantly favoured patients with a clinical benefit for those domains (except fatigue), as well as for role functioning, social functioning, pain, constipation and financial problems (Figures 4-5). For example, after 3 months of treatment the change in mean

score on the pain sub-scale was an improvement of -4.4 points on average for those with clinical benefit compared to a deterioration of 6.1 in those who had progressed by 3 months (p = 0.003).

Discussion

Anastrozole was associated with clinical benefit in 44% of patients with metastatic or recurrent ER and/PR positive endometrial cancer. Responses were durable in a small subset of patients and treatment was well tolerated in most patients. Importantly we also demonstrated that those patients who were categorized as having a clinical benefit based on RECIST response or stable disease at 3 months also had significant improvements in global QoL as well as several specific QoL domains compared to baseline scores, supporting the notion that these patients did indeed derive "clinical benefit". Reductions in the symptoms of pain and fatigue that can cause women significant distress were also seen, supporting the clinical benefit end-point based on the standard criteria of RECIST response /stable disease. The response rate of 7% (95% CI: 3-15%) is relatively low compared to other studies, but to the best of our knowledge this is the largest phase 2 trial of an aromatase inhibitor reported in a well-defined subset of patients with metastatic EC that were ER and /PR positive and had no prior hormonal therapy. The fact that there was evidence of clinical benefit in almost half the patients, with an associated improvement in HRQOL, underscores the importance of also including HRQOL endpoints in phase 2 trials to support the primary endpoint. "Clinical benefit" is now widely used as an endpoint in phase 2 trials and is based on the combination of disease stabilisation and

RECIST response and arguably HRQOL data should also be collected to back this up.

Importantly, anastrozole was well tolerated and one of the observations in this study was the apparently lower incidence of aromatase inhibitor (AI)-induced musculoskeletal events in women with EC cancers compared to these adverse effects reported by women with breast cancers. Studies in women on adjuvant aromatase inhibitors for early breast cancer reported 40-70% of treatment related arthralgia with 20-30% of patients stopping treatment early because of adverse effects [16-18]. In this study no patient stopped anastrozole for adverse effects. Given that many patients with endometrial cancer are older and frequently have co-morbidities related to obesity, the option of using a relatively non-toxic systemic therapy such as hormonal therapy is highly desirable.

It is not clear why the responses to aromatase inhibitors in endometrial cancer, are so much lower than in ER + ve breast cancer. There are a number of possible explanations including the high rate of alterations leading to overactivation of the PI3 kinase/AKT/MTOR pathway in Type 1 endometrioid endometrial cancers compared with breast cancers. These can lead to cross talk with other signalling pathways which can cause resistance to aromatase inhibitors[19, 20]. For example, activation of the AKT pathway due to alterations in PI3K, PTEN or AKT have been reported in over 90% of endometrial cancers. This can have variable affects on ERα transcriptional activity as well as blunting PR action in endometrial cancer. In addition, it is reported that ER and PR expression can be silenced by DNA methylation in endometrial cancer[21].

Combining agents that disrupt ER signalling such as aromatase inhibitors with PI3K/AKT/MTOR pathway inhibitors could potentially be synergistic and would be a rational combination to investigate in endometrial cancer. Of interest, more recent trials have reported promising results with the combination of an aromatase inhibitor and a MTOR inhibitor in endometrial cancer to try and overcome the effect of this pathway on endocrine resistance. Slomovitz et al reported a response rate of 35% in 35 patients treated with the combination of Letrozole and Everolimus, including 9 complete responses[10]. An on-going randomised trial (GOG 3007) is aiming to determine if this combination is more effective than the control arm of alternating tamoxifen and medroxyprogesterone. In addition, on-going trials are examining the efficacy of combined aromatase inhibitors and CDK 4/6 inhibitors in endometrial cancer.

The strengths of our trial include that women were selected based on having the target for the endocrine therapy present in their tumour, namely ER and/or PR. However, a limitation is that this was based predominantly on assessment of archival specimens at initial diagnosis. We do not know if ER and/or PR expression was still present in metastatic tumours. This may be important as a recent study reported that ER and PR median H-scores were significantly lower in metastases than in matched primary endometrioid endometrial cancers[22]. In addition, they found a higher frequency of hormone receptor gene promotor hypermethylation in metastases compared to matched primary tumours. These changes in hormone receptor expression in metastases may have important implications for treatment and argues for attempting to biopsy tumours prior to any hormonal therapy.

Although objective response rates were low, almost half of the patients derived clinical benefit with anastrazole as a single agent. It would be rational to continue to explore combining aromatase inhibitors with agents that inhibit other signal transduction pathways such as PI3K/AKT/MTOR as well as CDK4/6 in patients with ER/PR positive endometrial cancers. These are being considered in the PARAGON2 trial, with a greater emphasis and effort to collection of tumour specimens where possible at study entry and progression.

Figure legends

Figure 1: Study consort diagram

Figure 2: Clinical outcomes. (a) Progression-free survival for ITT population (n=84). (b) Progression-free survival for ITT population stratified by treatment free interval (n=78). (c) Progression-free survival beyond three month assessment point for those patients who gained clinical benefit (n=36), defined as complete, partial or stable disease at three month assessment.

Figure 3: Individual swimmers plot for each evaluable patient on study, colour coded by tumour grade: depicting time on treatment as well as time of partial response and/or progression

Figure 4: QLQ-C30 functioning domains and Global Health averaged on-study changes for months 1-3 by Clinical benefit status at 3 months.

Figure 5: QLQ-C30 symptom domains and financial problems averaged on-study changes for months 1-3 by Clinical benefit status at 3 months.

398 Table 1: Clinical Characteristics of 84 participating patients
399

		N	%
Age	Mean = 68	Range (36-89)	
ECOG performance status	0	40	48
	1	35	42
	2	9	11
Tumour grade	1	21	25
	2	33	39
	3	24	29
	Not available	6	7
FIGO stage	1	28	33
	2	13	16
	3	22	26
	4	15	18
	unknown	6	7
Prior chemotherapy	Yes	42	50
	No	42	50
Prior radiotherapy	Yes	56	67
	No	28	33
Treatment free interval†	<6 months	26	33
	6-12 months	13	17
	>12 months	39	50
IHC status	ER+/PR-	28	33
	ER+/PR+	52	62
	ER-/PR+	4	5

†Time since previous surgery/chemotherapy. 4 patients had no prior therapy, 2 had only Radiotherapy for which the date was not collected on the CRF.

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Table 2: Toxicity, data were available from 82 patients

Toxicity	Grade	N	%
Anorexia	1	18	22
	2	10	12
Headaches	1	12	15
Nausea	1	22	27
	2	10	12
Fatigue	1	33	40
	2	17	21
	3	7	9
Vomiting	1	10	12
	2	6	7
Hypercholesteraemia	1	1	1
	2	1	1
Alopecia	1	5	6
Hot flushes	1	35	43
	2	1	1
Rash	1	5	6
	2	1	1
Arthralgia	1	32	39
	2	7	9
Vaginal dryness	1	9	11

406 Table 3: QLQ-C30 averaged on-study changes for months 1-3 by Clinical Benefit
407 status at 3-months. Positive numbers represent improvements for the
408 functioning domains and Global Health, deterioration for the symptom domains
409 and financial problems.
410

	Clinical benefit at 3 months (N=34)		*Progressed by 3 months (N=35)*		*Clinical benefit - Progressed*	
Domain	*Mean (95% CI)*	*P**	*Mean (95% CI)*	*P**	*Difference (95% CI)*	*P†*
Physical Funct.	0.8 (-2.9 - 4.5)	0.656	-2.7 (-6.7 - 1.2)	0.172	4.6 (-0.7 - 9.8)	0.088
Role Funct.	3.8 (-5.5 - 13.0)	0.413	-4.8 (-10.1 - 0.4)	0.068	9.4 (0.6 - 18.3)	0.037
Emotional Funct.	7.7 (3.3 - 12.1)	0.001	0.0 (-3.8 - 3.8)	0.983	7.5 (2.8 - 12.3)	0.002
Cognitive Funct.	7.1 (1.2 - 13.0)	0.019	-5.6 (-12.3 - 1.0)	0.094	12.4 (4.4 - 20.3)	0.003
Social Funct.	10.5 (0.8 - 20.2)	0.036	-1.9 (-8.1 - 4.3)	0.537	12.8 (3.1 - 22.6)	0.011
Global Health	8.4 (4.1 - 12.7)	<0.001	-4.0 (-9.8 - 1.7)	0.158	12.8 (6.6 - 19.0)	<0.001
Fatigue	-4.0 (-11.4 - 3.4)	0.275	3.9 (-2.5 - 10.2)	0.226	-7.4 (-16.0 - 1.1)	0.087
Nausea Vomiting	0.9 (-2.7 - 4.5)	0.614	0.2 (-8.6 - 9.1)	0.957	-3.9 (-10.9 - 3.0)	0.260
Pain	-4.4 (-10.0 - 1.2)	0.120	6.1 (0.7 - 11.5)	0.028	-10.6 (-17.3 - -3.9)	0.003
Dyspnoea	1.5 (-5.7 - 8.6)	0.678	-0.6 (-7.7 - 6.4)	0.855	-0.6 (-9.8 - 8.7)	0.901
Insomnia	-2.5 (-10.6 - 5.7)	0.544	1.3 (-5.2 - 7.7)	0.691	-4.5 (-12.8 - 3.9)	0.290
Appetite Loss	-3.6 (-10.6 - 3.4)	0.303	3.0 (-5.9 - 11.9)	0.497	-5.2 (-15.0 - 4.6)	0.296
Constipation	-5.7 (-12.7 - 1.3)	0.107	2.5 (-7.9 - 12.9)	0.623	-9.2 (-18.2 - -0.2)	0.045
Diarrhoea	-2.6 (-10.2 - 4.9)	0.487	0.2 (-6.4 - 6.8)	0.961	-1.4 (-9.0 - 6.1)	0.703
Financial Problems	-8.8 (-15.7 - -2.0)	0.013	2.1 (-3.1 - 7.3)	0.425	-11.6 (-17.9 - -5.3)	<0.001

411
412 **Paired t-test*
413 *†Based on regression model including adjustment for baseline*
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