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Letrozole and Fulvestrant Combination in Second Line or More for Estrogen Receptor Positive Metastatic Breast Cancer; Efficacy and Predictive Factors of Response

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Abstract

Background: Preclinical data show that complete estrogen blockade by both down regulating estrogen receptor and inhibiting estrogen synthesis, has greater effect on tumor growth than either treatment alone. Combination of an aromatase inhibitor and fulvestrant may be an optimal second line therapy by preventing activation of growth factor pathways and possible cross talk with ER. One clinical study has shown no benefit of adding anastrozole to fulvestrant at first relapse. No clinical data on combination letrozole and fulvestrant in the second line or more metastatic beast cancer setting is available.

Methods: Estrogen receptor (ER) positive, progesterone receptor (PgR) positive or negative metastatic breast cancer patients with prior chemo and/or non-aromatase inhibitor (non-AI) endocrine therapy were treated with letrozole and fulvestrant. Patients with complete response(CR) partial response(PR), or stable disease(SD) were considered to have clinical benefit (CR+PR+SD). The predictive effects of age, number of prior regimens, ER/PgR status, histology, sites of metastatic disease were examined using Chi-square test.

Results: Thirty-two patients received oral letrozole 2.5 mg daily plus fulvestrant 250 mg intramuscular injection monthly. Mean age was 70 (range: 35-92), median number of prior treatments was 2 (range2-6). 25 pts had ER+/PgR+, 7 pts had ER+/PgR- tumors. Twenty-five patients had prior non-AI endocrine therapy. Eight patients had lobular histology. Overall clinical benefit rate was 71% (3 CR, 7 PR, and 13 SD). Mean duration of the clinical benefit was 15 months (range 2-38). Nine patients progressed under therapy. Age more than 65 versus younger (89% vs 46%, P=0.007), prior treatments less than 4 versus more (87% vs 25%, P=0.0007) and ER+/PgR+ versus ER+/PgR- (84% versus 42%, P<0.05) were predictive of clinical benefit; lobular histology, bone versus visceral metastases and prior endocrine therapy did not have affect clinical benefit rate (P>0.05).

Conclusions: In previously treated metastatic breast cancer patients, combination of letrozole and fulvestrant can be effective with a mean clinical benefit duration of 15 months. Older age, less than four prior lines of therapy, and expression of both ER/PgR are predictive of clinical benefit while lobular histology, site of metastatic disease and prior non-AI endocrine therapy are not. Letrozole and fulvestrant combination can be a reasonable option in selected group of previously treated metastatic breast cancer patients and should be further evaluated in larger studies utilizing recently approved high dose (500 mg) fulvestrant schedule.

Introduction

Endocrine therapy of breast cancer is a good example of the earliest targeted therapy for hormone receptor positive breast cancer. Historically it has included two main strategies in reducing the effects of estrogen on tumor growth; one by blocking estrogen from binding to its receptor and the other by inhibiting estrogen synthesis with aromatase inhibitors in the postmenopausal setting. The antiestrogen tamoxifen has been used since 1970s. However, tamoxifen exhibits both estrogen agonist and antagonist effects depending on its target tissue [1]. The search for a pure antiestrogen has led to the development of estrogen receptor down regulating agent fulvestrant. Fulvestrant binds to the estrogen receptor competitively, and in contrast to tamoxifen, it inhibits, and degrades the receptor [2-4]. Fulvestrant has demonstrated clinical efficacy with good tolerability when used as first, second, or third-line therapy in postmenopausal women with hormone receptor positive metastatic breast cancer [4-7]. Blocking both estrogen receptor and estrogen synthesis with a combination of pure antiestrogen and an aromatase inhibitor might have an additive effect. Preclinical data have shown greater inhibitory effect on tumor growth when fulvestrant and an aromatase inhibitor combined, as opposed to either treatment used alone on ovariectomized athymic mice bearing tumors of estrogen receptor positive human breast cancer cells [8-9]. Based on the theoretical advantage of utilizing fulvestrant in a lower estrogen

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environment, clinical studies evaluating the combination of aromatase inhibitors with fulvestrant have been under way. SWOG-S0226 is comparing anastrozole plus fulvestrant to anastrozole alone as first-line therapy in postmenopausal women. The SoFEA study has randomized hormone receptor positive locally advanced/metastatic postmenopausal breast cancer patients to fulvestrant, exemestane, or fulvestrant plus anastrozole, after failure of a non-steroidal aromatase inhibitor [10]. Results of these trials are eagerly awaited. So far, only one large clinical trial has reported results showing no benefit of adding anastrozole to fulvestrant at first relapse [11]. No clinical data on the effects of combination of letrozole plus fulvestrant in the second line or more have been reported in metastatic breast cancer patients. Here we present our data on the combination of letrozole plus fulvestrant in previously treated post menopausal hormone receptor positive metastatic breast cancer patients.

Patients and Methods

Patient eligibility

Previously treated postmenopausal women with histologically confirmed hormone receptor positive metastatic adenocarcinoma of the breast were eligible. Hormone receptor positive disease was defined as being positive for estrogen and/or progesterone receptors by the local institutional laboratory. Patients were required to have at least one prior chemo and/or non-AI hormonal therapy for metastatic disease. Additional inclusion criteria included at least one measurable lesion by response evaluation criteria in solid tumors (RECIST), age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status of zero to two and adequate organ and marrow function (leukocytes ≥3000/μl, absolute neutrophil count ≥1500/μl, platelet count ≥100 000/μl, total bilirubin ≤2.0 mg/dl, aspartate aminotransferase and/or alanine aminotransferase ≤2.5× institutional upper limit of normal, serum creatinine ≤1.5 mg/dl). Exclusion criteria included patients with no prior treatment for metastatic disease, major surgery or radiation therapy within the last 4 weeks, presence of rapidly progressive life-threatening metastases or uncontrolled comorbidities, and any active gastrointestinal disorder that altered motility or absorption.

Treatment plan

Patients received oral letrozole 2.5 mg once daily and fulvestrant 250 mg in a single 5-ml intramuscular injection every month which was defined as one cycle. At each monthly visit, patients underwent a history, physical exam, complete blood count, serum creatinine, electrolytes, liver function tests, and assessment of performance status, adverse events, and drug adherence. Treatment was continued without interruption until disease progression, or intolerable toxicity. Concurrent bisphosphonate therapy with an approved bisphosphonate was permitted for patients with bone metastases.

Evaluation of response and toxicity

All patients underwent computed tomography (CT) of the chest and abdomen and a bone scan within 4 weeks of registration. Tumor response was assessed every three cycles by CT using RECIST criteria, and bone scans were repeated if the original bone scan was positive or progressive bony metastatic disease was suspected. Toxicity was graded according to the National Cancer Institute Common Terminology for Adverse Events, version 3.0. The primary end point of the study was Clinical Benefit Rate, which was defined as objective response complete response (CR) plus partial response (PR) or stable disease (SD) in the absence of any new lesions. All patients were included in the efficacy and the safety analysis. Possible predictive factors for clinical benefit rate including age (more than 65 versus younger), number of prior treatments (less than 4 versus more), hormone receptor status (ER positive/ PgR positive versus ER postive/PgR negative), histology (lobular versus non-lobular), sites of metastatic disease (bone only versus visceral with or without bone) and presence or absence of prior non-AI endocrine therapy were evaluated by using Fisher's Chi-square test.

Results

Baseline characteristics of 32 patients are shown on (Table 1). Of 32 patients, 23 met the definition for clinical benefit including 3 patients with CR, 7 patients with PR, and 13 patients with SD, with a total clinical benefit rate of 71% (Figure 1). Nine patients progressed under therapy. Among those 23 patients who achieved clinical benefit 20 had prior non-AI endocrine therapy for metastatic disease. 16 of 23 patients who exhibited clinical benefit achieved best clinical response by 6 months and the remaining seven patients achieved their best response after 6 months. Mean duration of the clinical benefit was 15 months (range 2-38).

Age more than 65 versus younger (89% versus 46%, P=0.007), prior treatments less than 4 versus more (87% versus 25%, P=0.0007) and ER+/PgR+ versus ER+/PgR- (84% versus 42%, P<0.05) were predictive of clinical benefit; lobular histology, bone only versus visceral metastases with or without bone disease, and prior non-AI endocrine therapy did not predict clinical benefit (P>0.05), (Table 2).

There were no grade 3-4 toxicities. The most common grades 1-2 adverse events occurring in at least 5 % of patients included nausea (5%), fatigue (9%), anxiety (6%), hyperglycemia (6%), hypocalcemia (6%), and anorexia (6%). No patients discontinued treatments due to toxicity.

Baseline Characteristics	N	%
Patients enrolled	32	
Age at enrollment, years Mean Range	 70 35-92	
Race/Ethnicity	White	100
ECOG Performance Status 0 1 2	 2 11 19	 6 35 59
Sites of metastatic disease Bone only Visceral with/without bone	 12 20	 37 63
Hormone receptor status ER +/PR + ER +/PR -	 25 7	 78 22
Histology Lobular Non-Lobular	 8 24	 25 75
Prior metastatic therapy (endocrine and non-endocrine) Mean Range	 2 2-6	
Prior endocrine therapy (non-AI)	25	78

Table 1: Baseline Characteristics of Patients.

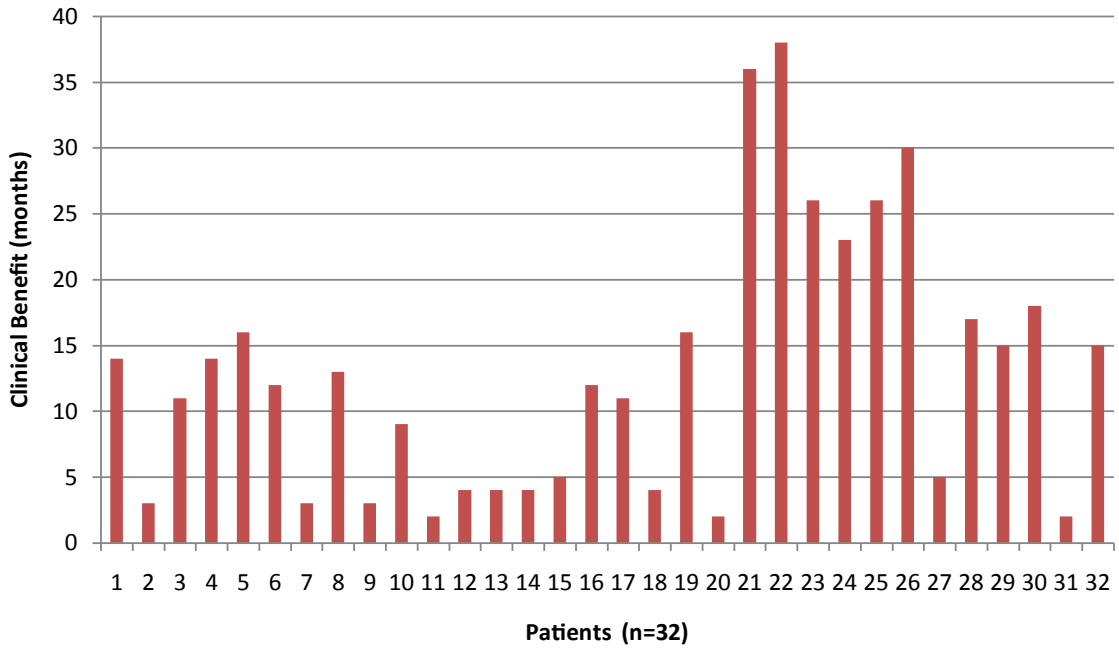

Figure 1: Clinical Benefit Rate of 32 patients while on letrozole +fulvestrant.

Discussion

While the beginnings of endocrine therapy for breast cancer, the first truly successful targeted therapy, can be traced to the 19th century, [12] the exact mechanisms of tumor response and resistance to endocrine manipulation still remain to be elucidated. Although several endocrine therapies, including selective ER modulators, aromatase inhibitors (AIs), progestins, androgens, and luteinizing hormone-releasing hormone (LHRH) agonists, and an estrogen receptor down regulator available today, the search for optimal endocrine agent, optimal combination, and optimal sequencing continues. Preclinical data have shown that complete estrogen blockade, by down regulating ER and inhibiting estrogen synthesis, has greater effect on tumor growth than either treatment alone [8,9]. Since the major source of estradiol in postmenopausal women is by aromatization of androgens, the combination of AIs with fulvestrant may enhance the efficacy of fulvestrant by reducing plasma estrogen levels. We evaluated the efficacy of combination therapy letrozole plus fulvestrant in 32 postmenopausal patients with hormone receptor positive metastatic breast cancer patients who had prior chemotherapy and/or non-AI endocrine therapy. The primary end point of our study was clinical benefit rate. We also looked for predictive factors of clinical benefit including age, number of prior treatments, hormone receptor status, histology, sites of metastatic disease, and prior non-AI endocrine therapy in this patient population. Our data show that combination of letrozole and fulvestrant can provide a meaningful and durable clinical benefit rate in this patient population. Older age, less than four prior lines of therapy, and expression of both ER/PgR are predictive of clinical benefit while lobular histology, bone versus visceral disease and prior non-AI endocrine therapy are not.

A number of ongoing or completed studies are trying to address the value of AI and Fulvestrant combination but so far no conclusive data are available. Massarweh [13] conducted a phase II trial to evaluate the efficacy of anastrozole/ fulvestrant/gefitinib as initial therapy in postmenopausal women with locally advanced or metastatic breast cancer. While the planned sample size was 60 patients, the trial was closed after 15 patients due to poor accrual. Of the 15 patients entered into the trial, 3 patients withdrew. Of the remaining 12 patients, 2 had a compete response, 5 had a partial response, 5 had stable disease, and 2 had progressive disease. Mrozek et al. [14] reported preliminary results of an ongoing phase II trial evaluating the combination of fulvestrant and exemestane in postmenopausal women with hormone receptor positive advanced breast cancer previously treated with chemotherapy, tamoxifen, or nonsteroidal AIs in the adjuvant or advanced disease setting. Patients received exemestane 25 mg starting on day 1, with fulvestrant 250 mg monthly added on day 8. At the time of the report, 19 women had been enrolled. Nine patients had a progression-free survival of more than 6 months (range: 6-20 months), with 8 of these patients still receiving treatment. An additional 8 patients had progression prior to 6 months. Accrual to this trial is ongoing.

So far the largest reported trial, FACT (Fulvestrant and Anastrozole in Combination Trial) randomized hormone receptor-positive metastatic breast cancer patients to the combination of the fulvestrant low dose regimen plus anastrozole versus anastrozole alone at the first relapse. There was no difference in time to progression and overall

Predictive Factor	Clinical Benefit %	P value
Age > 65 versus < 65	89 versus 46	< 0.007
Prior metastatic treatment ; < 4 versus > 4	87 versus 25	< 0.0007
Hormone receptor status ER+/PR+ versus ER+/PR-	84 versus 42	< 0.05

Table 2: Predictive Factors of Clinical Benefit.

survival [11]. Two other large phase III trials, Southwest Oncology Group (SWOG) SO226 and SOFAE (Study of Faslodex versus Exemestane with/without Arimidex), in postmenopausal women with metastatic breast cancer following progression on nonsteroidal AIs are currently ongoing. Both studies are utilizing the fulvestrant low dose regimen, 250 mg monthly injection. SWOG-S0226 will compare anastrozole to anastrozole plus fulvestrant as first-line therapy in postmenopausal women. SoFEA study has enrolled patients who have had disease progression after an aromatase inhibitor randomizing them to fulvestrant, exemestane, or fulvestrant plus anastrozole [10]. Results of these two large trials are eagerly awaited. Finally, Di Leo et al. [15] recently showed significantly improved clinical benefit of the fulvestrant high dose regimen compared to approved dose regimen in postmenopausal women with ER-positive tumors who were previously exposed to at least one endocrine therapy. The fulvestrant high dose regimen consisted of a 500 mg injection on day 1, day 14, and day 28, followed by monthly 500 mg injections thereafter.

Our data shows that letrozole and fulvestrant combination can be a reasonable option in a selected group of previously treated metastatic breast cancer patients. The efficacy of this combination even at low dose fulvestrant schedule is encouraging. Larger studies of this combination using high dose fulvestrant schedule is warranted.

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