Experience of Hormonal Therapy with Anastrozole for Previously Treated Metastatic Breast Cancer

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Abstract

Background: Recent years have brought significant progress to the development of hormonal therapies for the treatment of breast cancer. Several new agents have been approved for the treatment of breast cancer in the metastatic setting, among which is the new non-steroidal aromatase inhibitor, anastrozole, introduced for clinical use in Israel in March 1997.

Objectives: To evaluate the response rate and survival duration of patients treated with anastrozole for metastatic breast cancer, who had previously received at least one line of hormonal therapy.

Methods: Anastrozole was administered to 37 patients with metastatic breast cancer. The median age was 64 years. Estrogen receptor was positive in 20 patients, negative in 10 and unknown in 7. All patients were previously treated with tamoxifen in the adjuvant setting or as first-line hormonal therapy for metastatic disease. Anastrozole was given orally, 1 mg/day. Response was evaluated 2 months after the initiation of treatment and reevaluated every 2 months. Therapy was given until disease progression. Ten ER-negative patients were excluded from the final analysis.

Results: Twenty-seven patients were eligible for response and toxicity analysis. The median follow-up was 20 months. One patient (3.7%) achieved complete response and remains free of disease 28 months after start of therapy. No partial responses were seen. Twenty patients (74%) had stable disease. Two year actuarial survival was 57%. Median survival was 26.5 months after starting therapy and median progression-free survival was 11 months. The toxicity was mild: one patient (3.7%) complained of weight gain and one patient (3.7%) had mild fatigue.

Conclusion: Although the response rate was low, hormonal therapy with anastrozole seems to be beneficial in terms of disease stabilization, freedom from progression, and overall survival without serious toxicity.

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The first use of endocrine therapy for breast cancer can be traced to British surgeon George Beatson, who in 1896 described a young woman with recurrent breast cancer who responded to oophorectomy [1]. Today several endocrine therapies are available, including selective estrogen receptor modulators (tamoxifen and others), aromatase inhibitors, progestins, androgens and luteinizing hormone-releasing hormone agonists [2]. Clinical criteria predicting a greater likelihood of response to hormonal therapy are positive estrogen receptor and/or progesterone receptor, soft tissue metastases, longer disease-free interval, and increasing age. While the overall response rate is higher with chemotherapy than with endocrine therapy, the duration of response is somewhat shorter for chemotherapy-treated patients [3].

Tamoxifen has been the preferred first-line hormonal therapy for metastatic breast cancer for more than two decades because of its anti-estrogen effects in the breast tissue. The choice of second-line endocrine therapy after tamoxifen failure has been problematic. One option is the use of aromatase inhibitors, whose mechanism of action is suppression of peripheral conversion of androstendione to estrone [4].

The first commercially available aromatase inhibitor, aminoglutethimide, demonstrated activity in the metastatic breast cancer setting when compared with the progestational agent megestrol acetate [5], but resulted in bothersome side effects, like suppression of adrenal steroids synthesis, rash and lethargy. Aromatase inhibitors of a new generation (anastrolozole, vorozole and letrozole) lack the side effects of aminoglutethimide [6] and showed superiority over megestrole acetate and aminoglutethimide in randomized controlled studies in terms of both response and toxicity [7,8]. Anastrolozole was the first aromatase inhibitor of the new generation, approved for clinical use and introduced for practice in Israel in March 1997. The drug is given orally, 1 mg once daily. The present retrospective study aimed to evaluate response to anastrozole, toxicity and survival in unselected patients treated previously for metastatic breast cancer.

Patients and Methods

In 1997–98, 37 patients with metastatic breast cancer were treated with anastrozole. Patients' characteristics are presented in Table 1. The median age was 64 (range 30–86 years). Five patients were under age 50, but their menstrual cycle had ceased after previous chemotherapy and/or hormonal therapy. Eight patients (22%) had stage IV disease at presentation. Metastases were found as follows: bone in 28 patients (70%), skin and soft tissues in 10 (27%), lung in 9 (24%), liver in 3 (8%), lymph nodes in 3 (8%), brain in 2 (5%), and other sites in 3 (8%) patients. Sixteen patients (43%) had more than one metastatic site. ER was positive in 20 patients (54%) and negative in 10 (27%). Seven patients (19%) who had immigrated to Israel had received primary surgical treatment and adjuvant therapies in their countries of origin some years previously and their ER status was unknown. All patients had been previously treated with tamoxifen in the adjuvant setting or as first-line hormonal therapy for metastatic disease. Six patients (16%) had

ER = estrogen receptor

Table 1. Patients' characteristics

	No. of patients	%
Total no.	37	
Median age (yr)	64	
Estrogen receptor		
Positive	20	54
Negative	10	27
Unknown	7	19
No. of metastatic sites		
1	21	57
2	11	30
>2	5	13
No. of previous hormonal therapies	31	84
1	3	8
2	3	8
>2		

received more than one line of hormonal therapy. Twenty-eight patients (76%) received chemotherapy before anastrozole.

Anastrozole was given orally 1 mg/day until disease progression. Response was evaluated using National Cancer Institute criteria 2 months after the initiation of treatment and reevaluated every 2 months.

Results

Ten ER-negative patients were excluded from the final analysis, leaving 27 patients eligible for evaluation of response and toxicity. Sixteen patients (59%) had unmeasurable bone-only metastases. The median follow-up was 20 months. The toxicity was mild: one patient (3.7%) complained of weight gain and one patient (3.7%) had mild fatigue.

One 77 year old patient with lung metastases achieved complete response 4 months after starting treatment. She had undergone lumpectomy and axillary lymph node dissection in June 1987 and received no adjuvant systemic therapy. Lung metastasis was diagnosed in August 1996, and tamoxifen was given with a partial response. Anastrozole was started after disease progression in January 1998 and the patient remains disease-free 28 months after starting the therapy. No partial responses were seen. Twenty patients (74%) had stable disease. The median time to progression was 10.5 months.

Actuarial and progression-free survival is shown on Figure 1. One and two year actuarial survival was 78% and 57% respectively. One year progression-free survival was 44%. The median survival was 26.5 months and median progression-free survival 11 months.

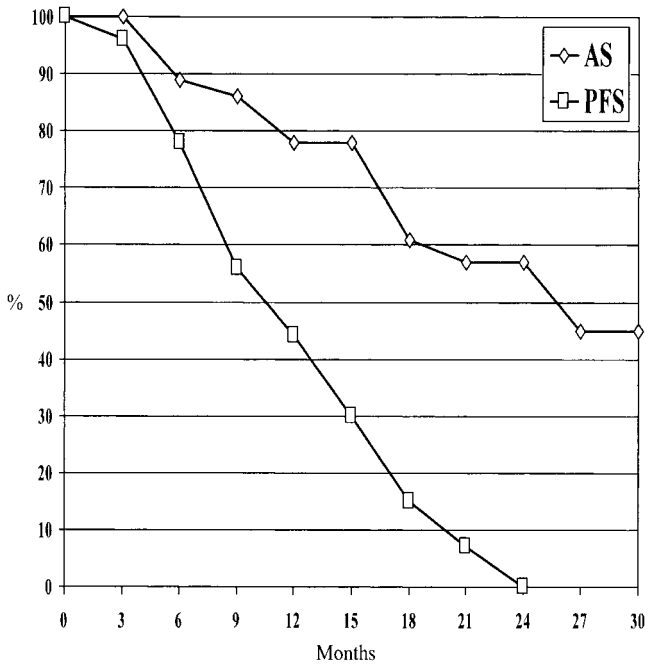

Figure 1. Survival of metastatic breast cancer patients after hormonal therapy with anastrozole. AS = actuarial survival, PFS = progression-free survival.

Discussion

Two randomized controlled trials compared anastrozole and megestrol acetate [7,8]. The response rate was 10% vs. 8% (not significant), median survival was 27 vs. 24 months (P=0.02) and median time to progression was 5 months for both drugs. The rate of weight gain was higher for medgestrol acetate (12% vs. 2%, P<0.05). Anastrozole given in a dose of 10 mg/day did not show any advantage over a standard dose of 1 mg/ day [7]. In our series only one patient (3.7%) had complete response and no partial responses were seen. The low response rate may be explained by the large proportion of patients with bone metastases in our study (70%). Response evaluation is complicated in such patients because they have non-measurable disease and cannot be assessed as partial responders (only complete response, stable disease and disease progression are possible outcomes) [7]. On the other hand, disease remained stable in 74% of the patients for a long period. The progression-free interval of 10.5 months and median survival of 26.5 months correspond with data presented in the literature [7,8].

Our study provides further evidence that the benefit of hormonal therapy with anastrozole for previously treated metastatic breast cancer lies in disease stabilization, overall and median survival, and freedom from progression without serious toxicity.

References

1. Beatson GT. On the treatment of inoperable cases of carcinoma of mamma: suggestion of a new method of treatment. *Lancet* 1896;ii:104–7.
2. Kimmic G, Muss HB. Current status of endocrine therapy for metastatic breast cancer. *Oncology* 1995;9:877–90.
3. Minton SE. New hormonal therapies for breast cancer. *Cancer Control* 1999;6:247–55.
4. Yue W, Wang JP, Hamilton CJ, et al. In situ aromatization enhances breast tumor estradiol levels and cellular proliferation. *Cancer Res* 1998;58:927–32.
5. Hoffken K. Experience with aromatase inhibitors in the treatment of advanced breast cancer. *Cancer Treat Rev* 1993;19:37–44.
6. Brodie AM, Njar VC. Aromatase inhibitors and breast cancer. *Semin Oncol* 1996;23:10–20.
7. Hamilton A, Piccart M. The third-generation of non-steroidal aromatase inhibitors: a review of their clinical benefit in the second line hormonal treatment of advanced breast cancer. *Ann Oncol* 1999;10:377–84.
8. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrole acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III studies. *J Clin Oncol* 1996;14:2000–11.

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