Therapeutic Activity of Testosterone in Metastatic Breast Cancer

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Abstract. *Background: Hormone therapy plays an important role in the management of breast cancer. In the past, testosterone was the most common line of hormonal therapy for this disease, but its use has been almost completely abandoned in the past 40 years. However, because of earlier reports on favorable therapeutic results, we re-evaluated its use for treatment of hormone-responsive patients who have become refractory to other lines of hormonal therapy. Patients and Methods: Fifty-three consecutive patients with positive metastatic breast cancer who had become refractory to treatment with other hormones and whose disease was progressing, were treated with testosterone propionate, 250 mg once every two weeks, twice, and then once every four weeks until disease progression, drug toxicity, or death. Results: Regression of disease was seen in 9 patients (17%; 2% complete and 15% partial). Stabilization of disease was seen in 22 patients (41.5%). In the remaining 22 patients (41,5%), the disease progressed. Median overall survival was 12 months from beginning of testosterone treatment. Hirsutism and dysphonia were noted occasionally, but were not distressing enough to mandate cessation of treatment. There was no major toxicity except for two non-fatal pulmonary emboli. Conclusion: Testosterone showed a significant therapeutic activity in previously hormone-treated patients with metastatic breast cancer who were no longer responding to such treatment and whose disease was progressing. These results warrant consideration of testosterone use as treatment for patients with hormone-sensitive metastatic breast cancer.*

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Excluding skin cancer, breast cancer is the most common malignancy among women, accounting for nearly 1/3 cases of cancer in the USA, and it is the second leading cause of cancer death among women. About 229,000 new cases of invasive breast cancer and 39,500 breast cancer deaths are expected to occur in US women in 2012 (1).

Endocrine therapy has been considered the most important systemic therapy for all stages of hormone-receptor-positive breast cancer for more than 100 years, since Beatson first made the link between the endocrine system and breast cancer and introduced oophorectomy (2). Breast cancer that expresses the estrogen receptor (ER) or the progesterone receptor (PgR) represents about 60% of all breast cancer in pre-menopausal women, and up to 80% in post-menopausal women (3-5).

Several decades ago, endocrine therapy was the most commonly ablative therapy (ovariectomy or adrenalectomy) in pre-menopausal women and additive therapy (androgen or estrogen administration) in post-menopausal women. Starting in the 1940s, androgen therapy was shown to induce regression of breast cancer metastases and to provide relief of pain in bone metastases from the disease, with minimal or no toxicity (6), but despite the fact that studies showed objective response rates sometimes exceeding 20% in patients with unknown hormone-receptor status (because that measurement was not common then) this treatment has been almost completely abandoned over the past 40 years; the estrogen antagonist tamoxifen has become the gold standard for first-line hormonal treatment of metastatic breast cancer. Subsequently, several alternatives to tamoxifen have become available: third-generation aromatase inhibitors (including anastrazole, letrozole, and exemestane), fulvestrant (an ER antagonist that down-regulates ER and PgR) and progestins. A major clinical problem limiting the usefulness of all endocrine therapy is the development of resistance in initially responsive tumors, with subsequent tumor progression and death.

In metastatic breast cancer, a hormone-sensitive patient usually undergoes several lines of treatment, often including various classes of endocrine agents, from tamoxifen to

progestagens, and often shows successive response to different drugs, but the use of androgens for treatment is very unusual nowadays despite the increasing interest in their role in the biology of breast tissue and the pathogenesis and growth of breast cancer (7, 8). In light of the earlier reports of therapeutic responses with androgen therapy (6), we conducted a retrospective study to assess the effectiveness and tolerability of testosterone treatment in a consecutive series of 53 patients with hormone receptor-positive breast cancer who had stopped responding following several lines of previous hormone therapy and whose disease was progressing.

Patients and Methods

Since September 2007, testosterone propionate (registered in Italy for treatment of metastatic breast cancer) has been used at the Oncology Unit of Reggio Emilia for the treatment of patients with ER/PgR-positive metastatic breast cancer whose disease was progressing despite several lines of previous hormonal treatment. In order to critically evaluate the efficacy and toxicity of this treatment, we retrospectively studied a consecutive series of 53 patients treated between September 2007 and November 2010. All patients were menopausal and their disease was progressing after a median of three lines of hormonal therapy (range 2-5) and a median of three lines of chemotherapy (range 0-11). Testosterone propionate, 250 mg intramuscolarly, was given once every two weeks, twice, and then once every four weeks until progression of disease, limiting toxicity, or death. The median duration of treatment was seven months, without dose reductions or delays. All patients had been previously responsive to at least one hormonal line of treatment and had received at least two such lines (among them, tamoxifen, anastrozole, letrozole, exemestane, fulvestrant, and megestrol); all had been treated with an aromatase inhibitor. Most of the patients had also been treated with several types of chemotherapy before beginning treatment with testosterone.

Date of birth, date of diagnosis of breast cancer and of metastatic disease, sites of disease, lymph-node involvement, histological type and grade, hormone-receptor status, proliferation rate, and HER2 status were obtained from clinical charts.

Hormone receptor status was defined as positive when the fraction of cells stained by the corresponding immunoreaction was more than 5%.

The proliferation rate was considered high when at least 15% of the cells were stained by the Ki-67 antibody.

Patients were considered to have HER2-positive disease if the primary or metastatic lesion had strong overexpression (3+) on immunohistochemistry or had gene amplification (ratio of HER2 to chromosome 17 copy number of more than 2 by fluorescence *in situ* hybridization.)

Sites of metastases were categorized as locoregional, visceral, or bone.

Evaluation of the extent of disease was usually made by spiral total-body computed tomography scan every three months.

The number of patients with clinical improvement was calculated by adding the number with complete regression of disease, the number with partial regression, and the number with stabilization for at least six months. Assessment of regression was made in accordance with RECIST, version 1.1 (9), and assessment of stabilization of disease was based on measurements from the start of treatment until the criteria for progression were met.

Table I. *Patients' characteristics*.

Number of patients	53
Age (median, range), years	68 (47-90)
Histotype	
Ductal	48 (91%)
Lobular	5 (9%)
HER2 status	
Negative	20 (38%)
Positive	5 (9%)
Unknown	28 (53%)
Ki67 status	
High	18 (34%)
Low	13 (25%)
Unknown	22 (41%)
Previous lines of endocrine or chemotherapy	Median 6, range 2-13
Site of metastases	
Visceral	23 (44%)
Bone	15 (28%)
Locoregional	15 (28%)

The Kaplan-Meier product limit method was used for survival analysis. SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA) was used in the data analyses. Overall survival was calculated from the first day of the first treatment for metastatic disease to the date of the last follow-up or death. Testosterone survival was calculated from the first day of testosterone treatment to the date of the last follow-up or death.

The adverse events were reported according to the common terminology criteria of the National Cancer Institute version 3.0 (10).

The study was approved by our local Ethics committee. All patients gave written informed consent before starting testosterone therapy, and at the time of data analysis all living patients gave another written informed consent for the use of their personal data in the study analysis.

Results

Patients' characteristics. The clinical and histopathological features of the population are shown in Table I. The median age of the patients was 68 years. Eastern Cooperative Oncology Group performance status was 0 to 1 for all patients. Fourty-eight patients had ductal infiltrating carcinoma and five were of the lobular infiltrating histotype. HER2 was assessed in 25 patients; it was positive in 5 and negative in 20. Dominant sites of disease were visceral, bone, and soft tissue in 44%, 28%, and 28% respectively.

Efficacy of treatment. Disease regression was seen in 9 patients (17%); regression was complete in 1 patient and partial in the other 8. Stabilization of disease was seen in 22

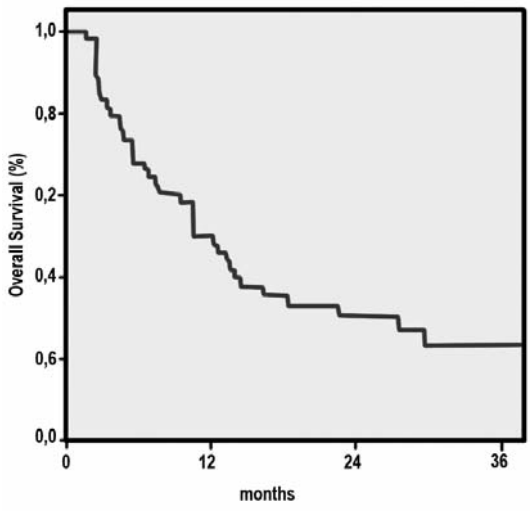

Figure 1. *Survival from the beginning of testosterone treatment.*

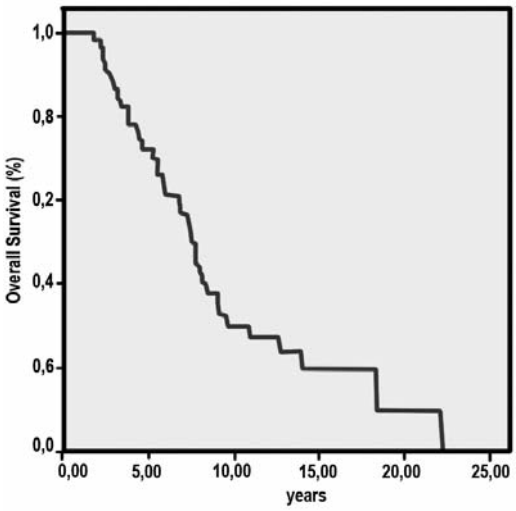

Figure 2. *Overall Survival*

patients (41.5%). The total number of patients with a favorable outcome (regression or stabilization) was 31 (58.5%). Progression of disease was seen in 22 patients (41.5%). The median survival with testosterone therapy, calculated from the first day of testosterone administration to the last day of follow-up or the day of death, was 12 months (95% confidence interval=9-14 months) (Figure 1). Median overall survival of the whole group, calculated from the first diagnosis of metastatic disease, was 7.5 years (Figure 2).

Toxicity. Toxicity in our group was minimal: Fatigue, depression, pruritus, and vaginal burning in one patient each; no patient had to discontinue treatment because of it. Hirsutism and dysphonia developed in 8% and 6%, respectively, of the patients but caused no psychological problems. Two patients developed pulmonary embolism requiring treatment with anticoagulants.

Discussion

Treatment of hormone receptor-positive metastatic breast cancer usually consists of chemotherapy with/without hormone therapy. Initial treatment with hormones alone is a reasonable choice for patients with slow-growing disease or with bone metastases only, but if visceral metastatic disease is present, hormone therapy is more likely to be given after chemotherapy. Patients with a response to therapy with one hormonal agent very often respond favorably to subsequent treatment with another one (11-14); for that reason, many patients are treated sequentially with several hormonal agents, including aromatase inhibitors, tamoxifen, fulvestrant, and megestrol (15). However, despite the availability of a number of effective hormonal therapeutic agents, almost all cases of metastatic breast cancer eventually become resistant to the hormones mentioned. Testosterone treatment is rarely given to such patients because it is currently considered obsolete, but we decided to re-evaluate that belief by conducting a retrospective, observational, single-center study of testosterone treatment in a consecutive series of patients with hormone-responsive metastatic breast cancer that was progressing after a median of three lines of hormone therapy (range 2-5) and three lines (range 0-11) of chemotherapy, with a median of six previous total lines of therapy (range 2-13).

The testosterone treatment proved to be significantly effective in our patients: disease regression occurred in 17% of our patients and stabilization of disease occurred in another 41.5%; thus 58.5% of our patients showed a favorable response. The median time-to-progression was seven months, which compares favorably with the time-to-progression seen with many aromatase inhibitors (16-18). Median survival was 12 months, which was gratifying and somewhat unexpected in light of the patients' advanced disease and non-responsiveness to other agents at this point. Because of the small size of the group, it was not possible to clearly delineate predictors of response to the testosterone therapy. We tried to evaluate two of the most common predictors of hormonal resistance: high Ki-67 (>15%) and HER2 positivity. Disease progression was observed in 61% of 18 patients with high Ki-67 and in 46% of 13 patients with low Ki-67, a suggestive but statistically non-significant difference; disease progression occurred in 3 out of 5 patients with HER2-positive disease and in 40% of 20 patients with HER2-negative disease, again a suggestive but statistically nonsignificant difference.

There are a number of limitations to our study: i) the group was quite small and was not selected randomly, although the fact that the cases were consecutive offers some hope that the selection may have been nearly random; ii) there were no controls (a controlled study of this type is probably ethically unacceptable), so that it is not possible to determine whether survival was meaningfully prolonged by testosterone therapy; iii) because of the retrospective nature of the study, quality-of-life questionnaires were not available, but there were many patients who reported an improvement in appetite, physical strength, and their sense of well-being. Despite these limitations, our results are encouraging: patients with clinical characteristics similar to ours have a short life-expectancy and are usually only candidates for palliative care; the apparently lengthened median survival of about one year with testosterone therapy would seem to warrant a prospective trial of such therapy.

Conflict of Interest

The Authors declare that they have no conflicts of interest.

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