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Testosterone Levels as a Marker of Prognosis to Goserelin Treatment in Metastatic Breast Cancer

G. Secreto, P. Boracchi, R. Buzzoni, E. Venturelli, A. Cavalleri and S. Dolci

Testosterone levels were measured in blood and urine of 35 premenopausal metastatic breast cancer patients before starting therapy with the gonadotrophin-releasing hormone (GnRH) analogue, goserelin. The aim of the study was to verify the reliability of testosterone measurement as a marker of prognosis. The time interval between starting therapy and progressive disease (time to progression) was chosen to assess prognosis. Univariate and multivariate analysis showed that only urinary testosterone levels were significantly associated with time to progression (Wald test 6.66, $P = 0.01$ for univariate and Wald test 7.93, $P = 0.0049$ for multivariate analysis), whereas no association was found for testosterone in blood. A statistical model is proposed to evaluate probability of progressive disease in relation to testosterone values in urine at different times. According to the model, the probability of progression decreases with increasing urinary testosterone values.

Key words: breast cancer, goserelin, marker of prognosis, testosterone
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INTRODUCTION

OOPHORECTOMY is usually the first-choice therapy for metastatic breast cancer in premenopausal women; it induces remission in 25–37% of unselected patients [1]. Treatment with long-acting gonadotrophin-releasing hormone (GnRH) analogues has been shown to be as effective [2, 3].

In previous papers [4–6], we reported that ovariectomy induced more frequent and longer-lasting remissions in women with higher than normal urinary testosterone excretion. In the present study, we investigated whether higher testosterone excretion and/or blood levels could also predict better response to the long-acting GnRH analogue, goserelin, as judged by the time to renewed progression after institution of goserelin therapy.

PATIENTS AND METHODS

40 premenopausal women, age 27–53 years, with metastatic breast cancer were recruited for the study. 5 were excluded, 2 for early progression during the first month of treatment and 3 because they were using corticosteroids. Of the 35 patients studied, 31 were given goserelin as the initial treatment upon relapse; 4 had had previous treatment, 3 with tamoxifen and 1 with chemotherapy, but these had been stopped at least 1 month before the start of this study.

Goserelin was given subcutaneously at a dose of 3.5 mg every 2 weeks for 2 months and then monthly until disease progression was noted, as defined by the standard WHO criteria [7].

A 12-h urine collection, 20.00–08.00 h, was obtained from each patient the night before starting therapy. The next morning, before therapy, blood was taken for determination of testosterone levels. Urinary testosterone was determined by gas chromatography [6], and testosterone in blood was measured by radioimmunoassay using a commercial kit (Sorin; Saluggia, Italy).

Statistical analysis

Urinary and serum testosterone were compared, using Spearman's r coefficient [8]. Time to renewed progression after the start of treatment was analysed with the Weibul regression model [9], in both univariate and multivariate contexts. Testosterone levels in blood and urine were treated as continuous variables, since any cut-off values are arbitrary.

Univariate analyses were performed to evaluate the prognostic roles of urinary and serum testosterone individually. The combined prognostic effect of the two together was evaluated by a multiple regression model. The additive contribution of each one, when added to the other, was evaluated by the likelihood ratio test [10]. Starting with the full model, a parsimonious regression model was obtained by a backward procedure [9]. The goodness of fit of the final model was determined by comparing, at 4-month intervals, the number of progressions observed with the number estimated by the model. The parameters of the final model were used to calculate the probability of progression in relation to testosterone levels at 12 months. Statistical analysis was performed with the SAS package [11].

RESULTS

Urinary testosterone excretion ranged from 0.23 to 18.3 μg/12 h. The 25th, 50th and 75th percentile values were 1.5, 2.3 and 3.25; only two values were above 5.0.

Serum testosterone ranged from 20 to 108 ng/dl. The 25th, 50th and 75th percentile values were 37, 47 and 68. There was

Correspondence to G. Secreto.
G. Secreto, R. Buzzoni, E. Venturelli, A. Cavalleri and S. Dolci are at the Endocrine Unit, National Cancer Institute, Via Venezian, 1, 20133 Milan, Italy; and P. Boracchi is at the University of Milan, Institute of Medical Statistics and Biometry, Via Venezian, 1-20133 Milan, Italy.
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Table 1. Time to progression in relation to testosterone levels: univariate and multivariate analysis

Model	Estimate	S.E.	Wald statistic	P
Univariate analysis				
Intercept	1.88	0.26	53.78	0.0001
Urinary testosterone*	0.26	0.10	6.66	0.01
Scale	0.76	0.11		
Intercept	2.13	0.41	27.56	0.0001
Serum testosterone	0.87	0.76	1.31	0.25
Scale	0.85	0.13		
Multivariate analysis				
Intercept	2.17	0.36	35.82	0.0001
Urinary testosterone*	0.29	0.10	7.93	0.0049
Serum testosterone	−0.73	0.65	1.25	0.26
Scale	0.73	0.11		
Contribution of each variable				
Urinary testosterone			13.39†	0.0003
Serum testosterone			1.10	0.2943

*Final model. †According to the likelihood ratio test.

only a weak, non-significant correlation between the blood and urine levels [rs = 0.429; standard error (S.E.) = 0.153].

The time to renewed progression showed a significant positive association with urinary testosterone excretion by univariate analysis (estimate 0.26; P = 0.01). No significant association was found with serum testosterone concentration (0.87; P = 0.25). In the multivariate analysis, only urinary testosterone excretion contributed to the overall association of testosterone levels with time to renewed progression (estimate 0.29; P = 0.0049; Table 1).

Using the backward selection process, the model considering only urinary testosterone excretion was more parsimonious and equally effective, compared with the model using both testosterone variables. The predicted relationship between testosterone excretion and the percentage of patients showing renewed progression at 12 months is depicted in Figure 1. A check for goodness of fit of the testosterone excretion versus the time to progression model gave satisfactory results: at each 4-month interval, the number of observed patients with progression was essentially the same as the predicted number. The probability of progressive disease at 12 months was 89% for near-zero testosterone excretion, 74% for excretion of 1.5 μg/12 h (25th percentile), 64% for excretion of 2.3 μg (50th percentile) and 52% for excretion of 3.3 μg (75th percentile). Although the curve predicts still lower percentages of progression with higher testosterone excretion, too few higher excretion values were observed to place any confidence on such predictions.

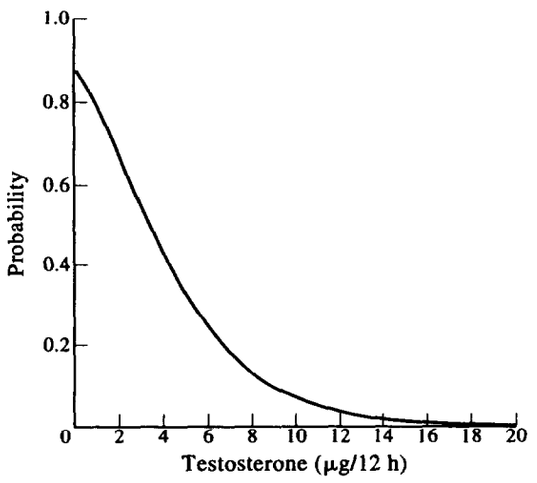

Figure 1. Probability of progression of disease at 12 months.

DISCUSSION

In the present study, the relationship between testosterone values and the time to progression was used as a marker of the general prognostic value of these parameters in metastatic breast cancer: a longer time to progression is often associated with objective remission; in some cases, stationary disease occurs without remission, but a longer stationary phase is a more favourable event than a brief objective remission followed by renewed progression.

What we found was that there was a strong positive association between higher urinary testosterone excretion and a longer time to progression during goserelin therapy. These results are similar to our earlier findings of a similar association between urinary testosterone excretion and the time to progression after oophorectomy. Thus, for both hormonal treatment modalities, higher urinary testosterone excretion is a favourable prognostic indicator of slower progression of the disease.

Interestingly, we found that serum testosterone levels did not show statistically significant prognostic power. Thus, the operative parameter of the effect of testosterone appears to be its production rate rather than its concentration in extracellular tissue fluids.

Clinicians are always asked to give a prognosis in cases of metastatic breast cancer. Our findings suggest that the measurement of urinary testosterone excretion may be useful in this regard.

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Peripheral Blood Progenitor Cell Transplantation Mobilised by r–metHuG–CSF (Filgrastim); a Less Costly Alternative to Autologous Bone Marrow Transplantation

C.A. Uyl-de Groot, D.J. Richel and F.F.H. Rutten

In a retrospective study, we calculated the treatment costs of 63 patients who received either autologous bone marrow transplantation (ABMT) with recombinant human granulocyte colony-stimulating factor (r–metHuG–CSF) (filgrastim) (n=13) or without r–metHuG–CSF (n=22) or alternatively, peripheral blood progenitor cell (PBPC) transplantation mobilised by r–metHuG–CSF (n=28). The recovery of granulocytes, platelets and reticulocytes after PBPC was markedly accelerated as compared with ABMT with or without r–metHuG–CSF. The accelerated haematopoietic recovery was associated with a reduction in platelets and red blood cell transfusion requirements, with a reduction in episodes of fever and with earlier discharge from the hospital. This resulted in the average cost per treatment of the PBPC group being almost 30% lower than the treatment costs in the ABMT groups.

Key words: costs, cancer, peripheral blood progenitor cells, autologous bone marrow transplantation, granulocyte colony-stimulating factor, filgrastim
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INTRODUCTION

BONE MARROW transplantation, as an adjunct to very intensive chemo- and radiotherapy, has significantly improved remission rates and survival in the treatment of acute leukaemias and malignant lymphomas. However, the procedure-associated risk of 5–15% fatal complications and the adverse effect on patients' morbidity can be serious due to a pancytopenic period of 3–4 weeks [1]. Moreover, the costs of autologous as well as allogeneic bone marrow transplantation are high, and the additional burden that these treatments place on hospital budgets raises concern [2, 3]. It is, therefore, relevant to not only assess the additional benefits to patients of new treatment options, but also to monitor their cost implications.

Haematopoietic growth factors make it possible to accelerate the haematopoietic recovery after an autologous bone marrow transplantation (ABMT) and thereby reduce the therapy-related toxicity. As a result, a reduction in the initial hospitalisation and in the number of days on intravenous antibiotics was demonstrated [4]. However, although the use of haematopoietic growth factors caused a shortening of the neutropenic period,

Correspondence to C.A. Uyl-de Groot.
C.A. Uyl-de Groot and F.F.H. Rutten are at the Institute for Medical Technology Assessment/Department of Health Care Policy and Management, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam; and D.J. Richel is at the Medisch Spectrum Twente, Dept. of Internal Medicine, P.O. Box 50.000, 7500 KA Enschede, The Netherlands.
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