Her2 and Progesterone Receptor Status Are Not Predictive of Response to Fulvestrant Treatment

Rupert Bartsch,[1] Catharina Wenzel,[1] Gabriela Altorjai,[1] Ursula Pluschnig,[1] Robert M. Mader,[1] Michael Gnant,[2] Raimund Jakesz,[2] Margaretha Rudas,[3] Christoph C. Zielinski,[1] and Guenther G. Steger[1]

Abstract

Purpose: It has been hypothesized that response to endocrine therapy for breast cancer depends on Her2 and progesterone receptor status, grading, and tumor proliferation rate. In this study, we evaluated factors that are potentially predictive of response and time to progression in patients treated with fulvestrant.

Experimental Design: One hundred fifty-five patients were included and followed prospectively. Patients received fulvestrant at standard dose by i.m. injection. Response was evaluated every 3 months using International Union Against Cancer criteria. Time to progression and overall survival were estimated with the Kaplan-Meier product limit method. A multivariate analysis was done to evaluate factors potentially influencing response and time to progression.

Results: We observed a partial response in 19 patients (12.3%), stable disease ≥6 months in 56 patients (36.1%), stable disease >3 months but <6 months in 7 patients (4.5%), and progressive disease in 73 patients (47.1%). Median time to progression was 5 months, and median overall survival was 27 months. Probability of achieving clinical benefit was significantly associated with a low proliferation rate ($P = 0.015$), nonvisceral metastatic sites ($P = 0.023$), and first-line therapy ($P = 0.023$). First-line therapy was also associated with prolonged time to progression ($P = 0.003$).

Conclusions: Response rate and time to progression are shown to be independent of Her2 status, grading, and progesterone receptor status. This is probably caused by the unique mechanism of action associated with fulvestrant: Due to receptor down-regulation, it blocks nuclear, cytoplasmatic, and membrane-bound estrogen receptor. Therefore, it seems to inhibit the cross-talk between growth factor receptor signaling and estrogen receptor in a more effective manner.

Breast cancer remains the main cause of cancer morbidity and mortality in women in most countries (1, 2). Although the clinical course of disease is highly variable, up to one third of patients with stage I and II disease are expected to experience tumor recurrence (3). Metastatic breast cancer remains an incurable disease. Today however, individualized, risk-adapted palliative treatment depending on tumor biology, symptoms, metastatic sites, time to disease recurrence, and patients' preferences has become available.

Endocrine therapy for breast cancer is the single best-established systemic treatment in this disease. With the identification of the estrogen receptor (ER), a predictive marker became available (4). Tamoxifen was the mainstay of hormonal therapy in early- and advanced-stage disease for approximately 3 decades. It acts as a selective ER modulator by blocking the AF-2 domain of ER but does not inhibit AF-1 activity (5). In the adjuvant setting, tamoxifen reduces recurrence rates by a relative 47% (6). The substance produces response rates of 17% to 27.1% as first-line therapy in advanced or metastatic disease (7–9). Still, *de novo* or acquired (secondary) resistance is the rule, with subsequent disease progression. In effect, only 50% of ER-positive tumors will respond to antiestrogens at first presentation (10).

Resistance to tamoxifen and other endocrine agents is believed to stem from a cross-talk between ER and growth factor receptors, along with their consecutive downstream signaling pathways. As a consequence, a ligand-independent activation of ER via the mitogen-activated protein kinase is possible (11). It has further been observed that increased activation of the phosphatidylinositol 3-kinase pathway and its downstream signal transduction molecules (especially phosphorylated AKT and mammalian target of rapamycin) is associated with decreased responsiveness to endocrine therapy, as this represents a major cell survival pathway (12, 13). Caused by this increase in growth factor signaling activity, estrogen loses its role as the driving force of tumor growth. It is therefore assumed that response to tamoxifen depends on Her2 status,

Authors' Affiliations: [1]First Department of Medicine and Cancer Centre, Clinical Division of Oncology, [2]Department of Surgery, and [3]Department of Pathology, Medical University of Vienna, Vienna, Austria

Received 12/22/06; revised 4/27/07; accepted 5/11/07.

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Requests for reprints: Guenther G. Steger, First Department of Medicine and Cancer Centre, Clinical Division of Oncology, Medical University of Vienna, 18-20 Waehringer Guertel, A-1090 Vienna, Austria. Phone: 43-1-40400-4426; Fax: 43-1-40400-6081; E-mail: guenther.steger@meduniwien.ac.at.

doi:10.1158/1078-0432.CCR-06-3050

progesterone receptor (PgR) status [as surrogate for increased growth factor signaling (14)], grading, and proliferation rate (15–18). Furthermore, a recent trial conducted by Rahko et al. (19) suggested that antiestrogen therapy might be insufficient in patients with tumors positive for mutant p53.

Novel endocrine treatment options include the third-generation aromatase inhibitors anastrozole and letrozole and the aromatase inactivator exemestane. Although more effective than tamoxifen (9, 20), there still is evidence to suggest reduced efficacy of these drugs in Her2-positive disease (15, 21, 22).

Fulvestrant is a new type of ER antagonist lacking agonist effects. The substance binds to the receptor, thus preventing dimerization and causing accelerated degradation of the ER-fulvestrant complex with loss of functional estrogen response. In turn, the increased rate of ER degradation leads to reduction in the cellular levels of PgR (23). Importantly, due to this mechanism, fulvestrant blocks nuclear ER as well as cytoplasmatic and membrane-bound ER, the latter two considered to be chiefly responsible for ER/growth factor pathway cross-talk (14, 24, 25).

Results from earlier trials suggested that patients with ER- and PgR-positive tumors may gain particular benefit from fulvestrant treatment (23, 26). Positive Her2 status was associated with lower remission rates, although no influence on the clinical benefit rate (CBR) was observed (23). Currently, no data are available to evaluate the potential activity of fulvestrant in the light of metastatic sites, proliferation rate, and p53 status. In this prospective analysis, we identified factors potentially influencing response rate and time to disease progression in breast cancer patients on fulvestrant treatment.

Materials and Methods

All data were collected at the First Department of Medicine and Cancer Centre, Clinical Division of Oncology, at the Medical University of Vienna, Vienna, Austria. One hundred fifty-five consecutive patients with metastatic breast cancer were included as eligible for fulvestrant therapy. Treatment was done in accordance with the ethical regulations of the Medical University of Vienna. Data were analyzed as of October 2006.

Patients. One hundred fifty-five consecutive patients (median age, 63 years; range, 30-88 years) were included and followed prospectively. All patients were evaluable for response and toxicity and were included in the intent to treat analysis. All of our subjects suffered from histologically confirmed metastatic breast cancer. Criteria for inclusion were as follows: presence of at least one measurable lesion, Karnofsky performance score ≥70%, life expectancy >3 months, adequate hematologic variables as defined by WBC count ≥3,500/μL, platelet count ≥100,000/μL, hemoglobin levels >9 g/dL, and adequate hepatic (serum bilirubin <1.5 mg/dL) and renal (serum creatinine <1.5 mg/dL) functions. For staging evaluations, computed tomography scans of the chest and the abdomen, mammography, and gynecologic examinations were mandatory. Patients with controlled metastatic disease to the brain (after whole brain radiotherapy, neurosurgical resection, and/or stereotactic radiosurgery of one to three metastases) were also eligible.

ER and PgR status were assessed by immunohistochemistry (ERα antibody, clone 1D5, and PgR antibody; Dako A/S), and receptor expression was estimated as the percentage of positively stained tumor cells. Results were given as +, ++, +++ positive staining or negative staining, with a cutoff value of <10% positive tumor cells.

Her2 status was assessed with the HercepTest (Dako A/S) or dual-color fluorescence *in situ* hybridization (FISH; PathVision HER2 DNA Probe kit, Vysis, Inc.). Tumors were classified as Her2 positive if they had a staining intensity of +++ on the HercepTest; if a score of ++ was gained, the tumors were reanalyzed using FISH. Tumors with Her2 gene amplification again were deemed Her2 positive.

Mutant p53 status was assessed by immunohistochemistry (ChemMate, Dako A/S). The scoring system was as follows: a nuclear staining >10% was scored positive for p53 status. Proliferation rate was estimated by the immunohistochemical assessment of nuclear antigen Ki-67 with MIB-1 antibody (Ki-67 antibody, clone MIB-1; Dako A/S). Ki-67 expression was estimated as the percentage of tumor cells positively stained by the antibody, with nuclear staining as criterion of positivity. We used a cutoff of ≥20% to define tumors with a high proliferation rate.

Table 1. Patient characteristics

Characteristics	Patients
Entered	155
Karnofsky performance score	80-100%
Age (y)	
Median (range)	63 (30-88)
Stage (initial diagnosis)	
Localized	92 (59.4%)
Advanced	43 (27.7%)
Not available	20 (12.9%)
Ductal carcinoma	117 (75.5%)
Lobular carcinoma	38 (24.5%)
Grading	
1	9 (5.8%)
2	91 (58.7%)
3	55 (35.55)
ER positive	146 (94.2%)
PgR positive	91 (58.75)
Double positive (ER positive + PgR positive)	82 (52.9%)
Her2 status (IHC/FISH*) positive	20 (12.9%)
p53-positive	27 (17.4%)
Ki-67 (≥20%)	51 (32.9%)
Adjuvant chemotherapy	69 (44.5%)
Adjuvant endocrine therapy	88 (56.8%)
Adjuvant aromatase inhibitor	6 (3.9%)
Palliative chemotherapy before fulvestrant	70 (45.2%)
Palliative endocrine therapy	130 (83.9%)
Tamoxifen	37 (28.5%)
Anastrozole/letrozole	114 (87.7%)
Exemestane	51 (39.2%)
Others	1 (0.8%)
Time to recurrence (mo)	
Median (range)	42 (3-336)
Treatment line	
First line	26 (16.8%)
Second line	74 (47.7%)
Third line	42 (27.1%)
Fourth line	13 (8.4%)
Metastatic sites	
Median (range)	2 (1-5)
Bones/soft tissue only	80 (51.6%)
Visceral only	13 (8.45)
Both	62 (40%)
Localization	
Lung	48
Liver	40
Bones	112
Lymph nodes	41
Soft tissue	60
Brain	2
Skin	23
Others	2
More than one metastatic site	104 (67.1%)

Abbreviation: IHC, immunohistochemistry.
*Immunohistochemistry, HercepTest; dual-color fluorescence *in situ* hybridization, PathVision HER2 DNA Probe kit.

Table 2. Toxicities (N = 155)

Toxicity	WHO grade			
	I	II	III	IV
Abdominal pain	1 (0.6%)	—	—	—
Headache	1 (0.6%)	—	—	—
Joint pain	1 (0.6%)	—	—	—
Nausea	4 (2.5%)	—	—	—
Vasomotor symptoms (hot flushes)	5 (3.2%)	1 (0.6%)	—	—
Weight gain	3 (1.9%)	—	—	—

Treatment plan and patient evaluation. All treatment was administered in an outpatient setting. Patients received fulvestrant at a dose of 250 mg every 4 weeks by i.m. injection. Response was evaluated every 3 months using International Union Against Cancer criteria.

Reevaluation of patients' tumor status was done with computed tomography scans of the chest and the abdomen with additional workup if indicated. Complete clinical response was defined as the disappearance of all measurable lesions for a minimum of 8 weeks. Partial clinical response was defined as ≥50% reduction in sum of products of the greatest diameters of measurable lesions, no increase of lesion size, and no new lesions. Stable disease was defined as <50% decrease and <25% increase with no newly emerging lesions. Progressive disease was defined as increase in tumor size exceeding 25% or the appearance of new lesions.

Clinical benefit was defined as the sum of benefit in patients experiencing complete clinical response plus partial clinical response plus stable disease ≥6 months.

Statistical analysis. Time to progression was defined as the interval from the first day of fulvestrant application until disease progression, and overall survival as the interval from first day of treatment until death of any cause. Data were analyzed as of October 2006. Time to progression and overall survival were estimated using the Kaplan-Meier product limit method. The log-rank test was used to test differences between time to progression and overall survival curves. P values of <0.05 were considered to indicate statistical significance. A Cox regression model was used to evaluate factors potentially influencing time to progression [grading (G_1, G_2, versus G_3)], ER status, PgR status, double-positive status (ER and PgR positive), Her2 status, localization of metastatic sites (bones and/or soft tissue only versus visceral), adjuvant endocrine therapy, adjuvant chemotherapy, palliative chemotherapy before fulvestrant, earlier endocrine therapy for metastatic disease, proliferation rate (Ki-67 <20% versus ≥20%), and p53 status]. The same factors were used in a multinomial logistic regression model to evaluate their potential influence on treatment response (clinical benefit versus progressive disease). Toxicity was evaluated according to WHO criteria and recorded per patient as worst episode recorded on one cycle of treatment.

All statistics were calculated using the Statistical Package for the Social Sciences 12.0 software (SPSS, Inc.).

Results

Patient characteristics. One hundred fifty-five consecutive patients (median age, 63 years; range, 30-88 years) suffering from advanced breast cancer were included. Fulvestrant was administered as first-line therapy in 26 patients (16.8%), second-line therapy in 74 patients (47.7%), third-line therapy in 42 patients (27.1%), and fourth-line therapy in 13 patients (8.4%), respectively. Table 1 lists the characteristics of the 155 patients included.

All patients received fulvestrant and were included in the intent-to-treat population for safety analysis; all individuals were also evaluable for efficacy analysis. Eighty-eight patients (56.8%) received prior adjuvant endocrine treatment (tamoxifen, 82; aromatase inhibitors, 6), and 130 (83.9%) prior palliative endocrine therapy of up to three therapy lines (tamoxifen, 37; aromatase inhibitors, 165; others, 1). Seventy patients (45.2%) had at least one earlier line of chemotherapy for metastatic disease.

Toxicity. Overall, fulvestrant was well tolerated. A total number of 1,353 injections was administered. Side effects are summarized in Table 2. Notably, no case of grade 3 or 4 adverse events was observed. Main toxicities consisted of vasomotor symptoms, weight gain, and headache; no injection site reactions were reported.

Efficacy. Median time of observation was 19 months (range, 3 to 58+ months). Nineteen patients had partial response [12.3%; 95% confidence interval (95% CI), 0.071-0.175], and stable disease ≥6 months was observed in 56 patients (36.1%; 95% CI, 0.285-0.437), stable disease >3 months but <6 months in 7 patients (4.5%; 95% CI, 0.012-0.078), and progressive disease in 73 patients (47.1%; 95% CI, 0.392-0.550), translating into a CBR of 48.4% (95% CI, 0.405-0.563). Corresponding figures for first line, second line, and beyond second line are given in Table 3. Median time to progression was 5 months (range, 2-34; 95% CI, 3.90-6.10; Fig. 1). Median overall survival was 27 months (range, 3 to 58+; 95% CI, 22.77-31.23).

Median time to progression was 16 months in first line (range, 3-34; 95% CI, 7.44-24.56), 5 months in second line (range, 3 to 29+; 95% CI, 3.65-6.35), and also 5 months in beyond second line (range, 2 to 29+; 95% CI, 3.40-6.60). The log-rank test revealed a significant difference (P = 0.004).

In the Cox regression model, fulvestrant as first-line treatment was significantly associated with prolonged time to progression (P = 0.003). A strong trend toward longer time to progression was observed with respect to tumors with a high proliferation rate. About tumors with low proliferation rate,

Table 3. Response rates (N = 155)

Number	Response					
	CR	PR	SD ≥6 mo	CBR	SD <6 mo	PD
Response overall (N = 155)	—	19 (12.3%)	56 (36.1%)	75 (48.4%)	7 (4.5%)	73 (47.1%)
Response						
First line (n = 26)	—	7 (26.9%)	13 (50%)	20 (76.9%)	—	6 (23.1%)
Second line (n = 74)	—	7 (9.5%)	23 (31.1%)	30 (40.5%)	5 (6.8%)	39 (52.7%)
Beyond second line (n = 55)	—	5 (9.1%)	20 (36.4%)	25 (45.5%)	2 (3.6%)	28 (50.9%)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

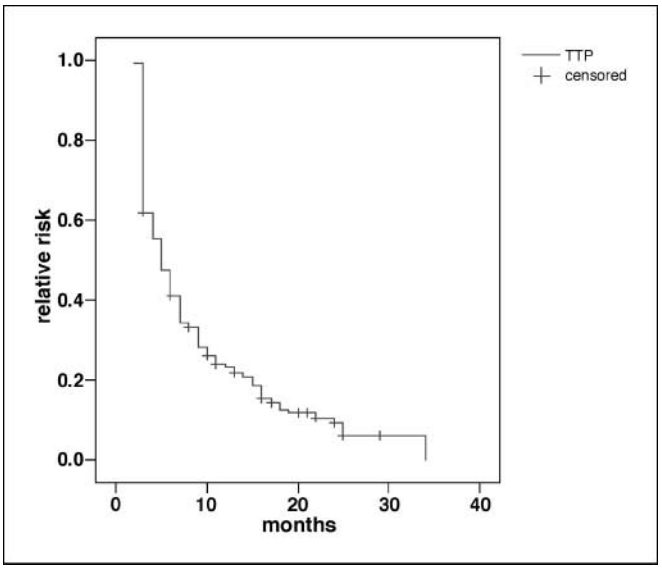

Fig. 1. Time to progression in 155 patients (months).

a strong trend toward longer time to progression was observed. This, however, did not reach statistical significance ($P = 0.061$). All other factors, including adjuvant therapy, grading, ER and PgR status, Her2 status, location of metastases, earlier adjuvant or palliative chemotherapy, adjuvant endocrine therapy, and mutant p53 positivity, had no significant effect on time to progression.

The probability of achieving a clinical benefit from fulvestrant was significantly associated with proliferation rate ($P = 0.015$), first-line therapy ($P = 0.023$), and localization of metastatic sites ($P = 0.023$). Patients with slowly proliferating tumors, nonvisceral metastases only, and those receiving fulvestrant as first-line therapy had a higher probability of achieving clinical benefit. There was no significant influence of any other factor (grading, adjuvant therapy, ER and PgR status, Her2 status, earlier adjuvant or palliative chemotherapy, adjuvant endocrine therapy, and mutant p53 status). Results of the multivariate analysis are summarized in Table 4.

Discussion

Fulvestrant is an effective treatment option in advanced breast cancer with a favorable toxicity profile. We observed a response rate of 12.3% and stable disease ≥6 months in 36.1% of patients, resulting in a 48.4% CBR. Time to progression on fulvestrant as first-line therapy was superior when compared with beyond first line. This result was expectable and is commonly observed in metastatic breast cancer. In the multivariate analysis, longer time to progression was predicted by first-line treatment, whereas a strong trend was observed for low proliferation rate; CBR was significantly associated with first-line therapy, low proliferation rate, and nonvisceral metastatic sites.

Due to an increased utilization of fulvestrant in the neoadjuvant setting and in patients with nonsymptomatic visceral disease, markers potentially predicting for primary resistance to therapy are of value. In those individuals, nonresponsiveness is potentially life threatening. This circumstance evidences the value of our results.

Data from the present investigation need to be discussed in the light of existing evidence of factors potentially predicting for response to other endocrine agents.

In view of preclinical and clinical studies, it seems reasonable to suggest tamoxifen resistance in Her2-positive disease (17). Furthermore, patients with high-grade tumors, tumors with high proliferation rates, and PgR-negative disease might derive less benefit from selective ER modulators (16, 17). As underlying mechanism, a cross-talk between the ER pathway and cell cycle and survival pathways has been postulated (25, 27). This cross-talk is bidirectional; modulation of the ER pathway influences growth factor pathways and vice versa (28). Consequently, tumor growth is regulated via pathways not under direct control of ER. Such pathways, crucial for both tumor cell proliferation and modulation of ER activity include the Her2 pathway, cell survival phosphatidylinositol 3-kinase/AKT pathway, cell proliferation pathway mediated by mitogen-activated protein kinase, and the stress-induced c-Jun NH_2-terminal kinase pathway (29).

Unlike data referring to tamoxifen, the factors potentially predictive of response to aromatase inhibitor treatment are not well established. Data from studies evaluating treatment response in Her2-positive and Her2-negative disease are conflicting throughout the literature (15, 21, 22, 30). Still, according to available information, and in the light of the fact that growth factor receptor signaling can cause ER activation even in the absence of estrogen, a decreased treatment benefit in Her2-positive disease must be presumed.

Fulvestrant activity, in contrast, does not seem to be reduced in grade 3 tumors. Furthermore, PgR negativity, which serves as a surrogate for increased growth factor pathway signaling in Her2-negative disease (14), had no significant influence. Most importantly though, Her2 status neither reduced the probability of achieving clinical benefit nor was it associated with shortened time to progression. This might be caused by the unique mechanism of action of the agent. Due to receptor down-regulation, fulvestrant blocks nuclear, cytoplasmatic, and membrane-bound ER. As the latter two factors are held responsible for the above-mentioned cross-talk, it is hypothesized that fulvestrant more effectively blocks this escape mechanism than other endocrine treatment options (14, 24, 25).

Data about decreased efficacy in tumors with high proliferation rates and visceral disease are well in line with data from

Table 4. Results—multivariate analysis ($N = 155$)

Factor	TTP	CBR
Grading	n.s.	n.s.
ER status	n.s.	n.s.
PgR status	n.s.	n.s.
ER + PgR (double positive) status	n.s.	n.s.
Her2 status	n.s.	n.s.
Proliferation rate	n.s.	$P = 0.015$
Mutant p53 status	n.s.	n.s.
Localization of metastatic sites	n.s.	$P = 0.023$
Adjuvant endocrine therapy	n.s.	n.s.
Adjuvant chemotherapy	n.s.	n.s.
Earlier palliative endocrine therapy	$P = 0.003$	$P = 0.023$
Earlier palliative chemotherapy	n.s.	n.s.

Abbreviation: n.s., not significant.

various other studies (18). It may therefore be stated that chemotherapy is more advisable for patients with symptomatic visceral disease and/or those with rapidly growing tumors.

In our trial, mutant p53 positivity influenced neither CBR nor time to progression. Although several trials have presented inconclusive results about p53 and response to chemotherapy (31), data on endocrine treatment are scarce. Rahko et al. suggested that antiestrogen therapy is insufficient in mutant p53-positive patients (19). In most of these studies (including our own), p53 status was assessed by immunohistochemistry. Of note, several p53 mutations are not associated with enhanced staining. Furthermore, by means of immunohistochemistry, wild-type p53 cannot be differentiated from total p53 loss (31). Therefore, no definitive statements are possible.

We conclude that fulvestrant is an effective treatment option in endocrine-responsive advanced breast cancer. Similar to other endocrine substances, it is most effective in first-line therapy and in tumors with low proliferation rates. Unlike those substances, its efficacy does not depend on PgR and Her2 status, which may be explained by the unique mechanism of action of the agent. Fulvestrant should therefore be considered an option of choice for trials evaluating the combination of endocrine treatment and targeted therapies.

Acknowledgments

We thank Karl Thomanek for his support in drafting the manuscript.

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