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Progesterone Receptor Activity and the Response to the First Endocrine Therapy in Advanced Breast Cancer

JOHN M. RAEMAEKERS,* LOUK V. BEEX,* GERLACH F. PIETERS,* ANTHONY G. SMALS,* THEO J. BENRAAD,† PETER W. KLOPPENBORG* and THE BREAST CANCER STUDY GROUP‡

**Department of Medicine, Division of Endocrinology, †Department of Experimental and Chemical Endocrinology, ‡Department of Surgery* (Dr. T. Wobbes), *Department of Radiotherapy* (Dr. W. v. Daal), *Department of Medical Oncology*, (Dr. D. Wagener), *Department of Pathology* (Dr. R. Holland), *and Department of Radiology* (Dr. J. Hendriks), *University Hospital, Nijmegen, Nijmegen, The Netherlands*

Abstract—*The predictive value of the progesterone receptor activity (PgR) was studied in a group of 84 patients with estradiol receptor (ER) positive advanced breast cancer who received their first endocrine treatment (tamoxifen or ovariectomy), with special emphasis on the timing of the receptor analysis. All patients were treated at 1 center and receptor analyses performed in 1 laboratory. In the group of 27 patients with PgR analysis performed immediately prior to the start of treatment, 14 out of 18 PgR+ve and only 2 out of 9 PgR−ve patients responded ($P < 0.02$). In contrast, when PgR was analysed > 6 months prior to the start of treatment, the response rates for PgR+ve and PgR−ve patients did not differ significantly: 55% vs. 33% respectively. With regard to quantitative rather than qualitative PgR data, PgR levels exceeding 100 fmol/mg protein irrespective of ER levels, are an excellent indicator of hormonal responsiveness with a response rate of more than 80%, even if PgR analyses are performed long before the start of treatment.*

INTRODUCTION

THERE is still no consensus whether measurement of the progesterone receptor activity (PgR) in tumor tissue adds to the predictability of hormonal responsiveness of advanced breast cancer as assessed by measuring the estradiol receptor activity (ER). By combining the data of 14 studies, Sedlacek and Horwitz [1] showed that patients with ER+ve PgR+ve tumors will respond to endocrine therapy in about 70% of the cases whereas the patients with ER+ve PgR−ve tumors do so in about 30%. The response rates in the individual studies varied considerably and several authors found no additional predictive value for PgR compared to ER alone [2–5]. Recent work in several laboratories, including ours, indicates that the predictive value of PgR might be hampered by the considerable inconsistency of PgR when analysed sequentially in the course of the disease [6–9]. Stewart *et al.* [4] suggested that the analysis of PgR is only useful when carried out immediately before the start of treatment. However, the subgroups of patients in their study differed significantly in several prognostic variables (i.e. age, menopausal state, disease-free interval, site of metastasis). Therefore, the authors themselves stated that firm conclusions could not be drawn. We restudied the clinical usefulness of the qualitative PgR analysis in predicting hormonal responsiveness in a group of patients with ER+ve advanced breast cancer. Special attention was paid to the interval between the PgR analysis and the start of the endocrine treatment. Furthermore, since the distinction between receptor positivity and negativity is a simplification of the continuous variable that receptor concentration really is, we additionally examined whether quantitative PgR data is a better indicator than the merely qualitative PgR status, as was established earlier for ER by Paridaens *et al.* [10].

PATIENTS AND METHODS

PgR was analysed in tumor specimens of 84 patients with ER+ve breast cancer. All patients

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Address reprint requests to: J.M.M. Raemaekers, Dept. of Medicine, Div. of Endocrinology, St. Radboud University Hospital, Geert Grooteplein 8, Nijmegen, The Netherlands.
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received their first endocrine therapy and were treated at our breast clinic by the same physicians. The results of ER and PgR analyses were available before the start of the endocrine treatment. Twenty-one of the 84 patients had received prior adjuvant chemotherapy (a combination of cyclophosphamide, methotrexate and 5-fluorouracil). The first endocrine therapy was either tamoxifen (20 mg orally twice daily: pre-menopausal $n = 3$; post-menopausal $n = 68$) or surgical oophorectomy (pre-menopausal $n = 13$). Before the start of the endocrine therapy all patients had a full physical examination with measurements and/or photographs of visible lesions, complete blood counts and biochemical screening, a chest X-ray, a bone scan and radiographs of the areas with increased uptake. Liver scans or upper abdominal echographic examinations were performed only if liver metastases were suspected clinically and/or biochemically. Patients were followed at the out-patient clinic at regular intervals, usually monthly. All patients were evaluated for the response to the treatment 3 months after the start of the therapy. The response to the endocrine treatment was assessed, always by the same physician and an experienced rontgenologist, according to the UICC criteria [11]. The patients whose tumors showed neither an objective remission nor a failure to the treatment, were considered to have stable disease and are included in the analysis as 'no-remission'. After more prolonged observation periods these patients were reassessed. One patient had progressive disease after 4 months of therapy, whereas the remaining 4 patients were still classified as having stable disease after reassessment (duration of stable disease being 7, 8, 13 and 42 months respectively). Patients with non-assessable lesions (such as pleural effusions) whether or not other assessable lesions were present were considered not evaluable and as a consequence excluded from this study. The menopausal state was defined as post-menopausal when menses had ceased for at least 12 months or when ovariectomy had been performed earlier.

The ER and PgR assays were all performed in the same laboratory on histologically-proven breast cancer tissue using the dextran-coated charcoal method with multiple-point Scatchard-plot analysis, as described earlier [12]; levels > 10 fmol/mg protein were considered receptor positive (both ER and PgR) (dissociation constant $K_D < 2$ nM).

For all the assays the minimum cytosol protein concentration was 2 mg/ml cytosol.

Statistical analysis was performed using Fisher's Chi-Square test (P denoted by P) and Wilcoxon's Two-sample test (P denoted by P^*).

RESULTS

Qualitative PgR data and the response to the first endocrine treatment

In the group of 84 patients with ER+ve advanced breast cancer, 52 patients (62%) had a PgR+ve tumor whereas the remaining 32 patients (38%) lacked PgR in their tumor tissue.

Forty-one out of the 84 patients (49%) showed an objective remission to the first endocrine therapy. Five patients had stable disease and the remaining 38 patients had progressive disease during the therapy. Table 1 shows the clinical characteristics of both groups. The qualitative PgR status of the tumor was the only significant discriminant between both groups: about 60% of the PgR+ve patients showed an objective remission vs. 31% of the PgR−ve patients ($P < 0.02$). Table 2 illustrates that there were no imbalances in the clinical characteristics between the patients with PgR+ve and PgR−ve tumors.

Table 3 shows the data on the response to the treatment related to the timing of the PgR analysis. When PgR was analysed immediately prior to the start of the treatment, 78% of the patients with ER+ve PgR+ve tumors responded whereas only 22% of the patients with ER+ve PgR−ve tumors showed an objective remission ($P < 0.02$). In contrast, when the interval between the PgR analysis and the start of the treatment exceeded 6 months, the PgR status did not add to the predictive value of ER ($P > 0.1$). In these subgroups of patients no significant differences were noted between the PgR+ve and PgR−ve patients in any of the clinical characteristics (data not shown). Table 3 further shows that a similar impact of the timing of the receptor analysis was not found for ER. When the 21 patients who received prior adjuvant chemotherapy were excluded from this analysis similar data were obtained: in the 'immediately-prior' group 91% (10/11) of the ER+ve PgR+ve patients and 28% (2/7) of the ER+ve PgR−ve patients responded ($P < 0.03$) whereas in the '> 6 months-prior' group no significant difference was found between the PgR+ve and PgR−ve patients: 13 out of 22 responded in the former vs. 6 out of 12 in the latter ($P > 0.1$).

Quantitative PgR data and the response to the first endocrine treatment

Table 4 shows the clinical characteristics of the 27 patients with ER+ve PgR+ve tumors with PgR analyses performed > 6 months prior to the start of treatment. It appeared that the quantitative PgR levels were the only significant discriminant between the responders and the non-responders: the mean PgR level for the former was 295 fmol/mg protein and for the latter 87 fmol/mg protein

Table 1. Clinical characteristics of the 84 patients with ER+ve advanced breast cancer receiving their first endocrine treatment

		Remission $n = 41$ (%)	No remission $n = 43$ (%)	P
Age (year)	Mean ± S.D.	61 ± 13	59 ± 11	> 0.1
Menopausal state	Pre-	10 (24)	6 (14)	
	Post-	31 (76)	37 (86)	> 0.1
DFI (months)	Mean ± S.D.	41 ± 35	34 ± 23	> 0.1
Dominant site	Soft	7 (18)	8 (19)	
of metastases	Bone	17 (41)	19 (44)	> 0.1
	Visceral	17 (41)	16 (37)	
Prior adjuvant	Yes	7 (17)	14 (32)	
chemotherapy	No	34 (83)	29 (68)	> 0.1
Site of receptor	Primary	24 (58)	20 (47)	
analysis	Recurrence	17 (42)	23 (53)	> 0.1
PgR status	Positive	31 (76)	21 (49)	
	Negative	10 (24)	22 (51)	< 0.02

Table 2. Clinical characteristics of the 84 patients with ER+ve advanced breast cancer related to the PgR status of the tumor

		PgR+ve $n = 52$ (%)	PgR−ve $n = 32$ (%)	P
Age (year)	Mean ± S.D.	60 ± 13	60 ± 11	> 0.1
Menopausal state	Pre-	11 (21)	5 (16)	> 0.1
	Post-	41 (79)	27 (84)	
DFI (months)	Mean ± S.D.	38 ± 31	36 ± 26	> 0.1
Dominant site	Soft	11 (21)	4 (12)	
of metastases	Bone	21 (40)	15 (47)	> 0.1
	Visceral	20 (39)	13 (41)	
Prior adjuvant	Yes	12 (23)	9 (28)	> 0.1
chemotherapy	No	40 (77)	23 (72)	
Site of receptor	Primary	27 (52)	18 (56)	> 0.1
analysis	Recurrence	25 (48)	14 (44)	

Table 3. Timing of receptor analysis and the response to the first endocrine treatment

	ER+ PgR + $n = 52$ remissions/totals		ER+ PgR− $n = 32$ remissions/totals	All $n = 84$ remissions/totals
Immediately prior	14/18	$P < 0.02$	2/9	16/27
1–6 months prior	2/7	N.S.	2/5	4/12
> 6 months prior	15/27	N.S.	6/18	21/45

($P^* < 0.02$). Figure 1 shows the individual ER and PgR levels of the responding and non-responding patients. At PgR levels > 100 fmol/mg protein the number of patients with an objective remission was significantly higher than at the lower levels: 83% (10/12) vs. 33% (5/15) respectively ($P < 0.04$).

At PgR levels > 300 fmol/mg protein all patients responded. Due to the overlap in the quantitative ER data, discrimination between responding and non-responding patients was not possible by regarding the ER levels.

Figure 2 illustrates the impact of combining quantitative ER and PgR data. Quantitative PgR data proved to be superior to the quantitative ER data in predicting the response: at PgR levels exceeding 100 fmol/mg protein 10 out of 12 patients

Table 4. Clinical characteristics of the patients with PgR analysis performed > 6 months prior to the start of the first endocrine treatment

		Remission $n = 15$ (%)	No remission $n = 12$ (%)	P
Age (year)	Mean ± S.D.	60 ± 15	61 ± 10	> 0.1
Menopausal state	Pre-	5 (33)	0 (0)	> 0.1
	Post-	10 (67)	12 (100)	
DFI (months)	Mean ± S.D.	31 ± 18	32 ± 20	> 0.1
Dominant site of metastases	Soft	2 (13)	0 (0)	> 0.1
	Bone	9 (60)	6 (50)	
	Visceral	4 (27)	6 (50)	
Prior adjuvant chemotherapy	Yes	2 (13)	3 (25)	>0.1
	No	13 (87)	9 (75)	
Site of PgR analysis	Primary	13 (87)	8 (67)	> 0.1
	Recurrence	2 (13)	4 (33)	
Quantitative ER fmol/mg protein	Mean ± S.D.	184 ± 246	214 ± 266	> 0.1
Quantitaitve PgR fmol/mg protein	Mean ± S.D.	295 ± 237	87 ± 72	< 0.02

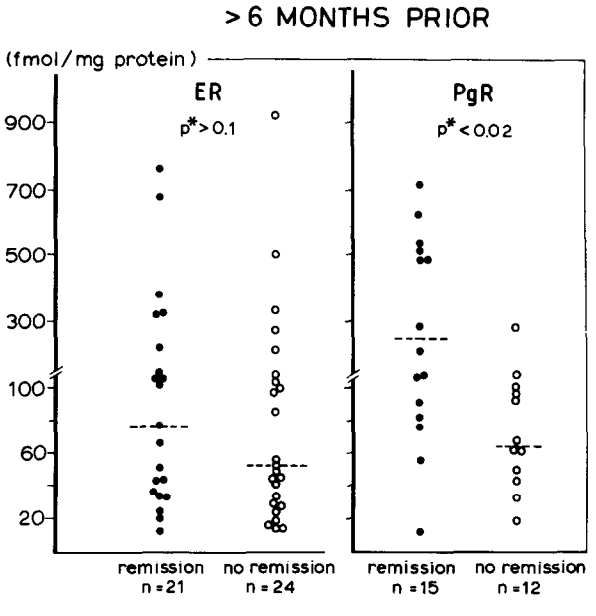

Fig. 1. Quantitative ER and PgR data and the response to the first endocrine treatment. All receptor analyses performed > 6 months prior to the start of the treatment.

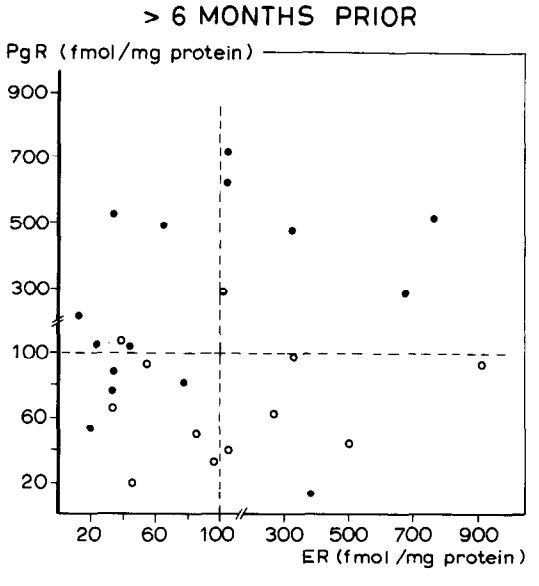

Fig. 2. Combined quantitative ER and PgR data and the response to the first endocrine treatment. All receptor analyses performed > 6 months prior to the start of the treatment. ●: objective remission. ○: no remission.

responded irrespective of the quantitative ER levels whereas only 1 out of 6 patients with PgR levels < 100 fmol/mg protein but ER levels > 100 fmol/mg protein responded ($P < 0.03$). The numbers of patients in the groups with PgR analyses performed immediately prior or between 1 and 6 months prior to the start of the treatment, were too small to permit a statistical analysis.

DISCUSSION

The present study clearly demonstrates that both the qualitative as well as the quantitative analysis of PgR significantly improves the predictability of hormonal responsiveness in patients with ER+ve advanced breast cancer.

When the qualitative PgR status of the tumor is assessed immediately prior to the start of the first endocrine treatment, 78% of the patients with ER+ve PgR+ve tumors shows an objective remission whereas only 22% of the patients with ER+ve PgR−ve tumors respond. In contrast, PgR does not add to the predictive value of ER when PgR analysis is performed > 6 months prior to the start of the treatment. Roughly, these results reconfirm the preliminary suggestions of Stewart *et*

al. [4]. It has to be noted that unlike their study, no imbalances in clinical characteristics between the various subgroups of patients were noted. Since tumor tissue is not infrequently inaccessible for performing a biopsy with analysis of PgR, we took special interest in the predictive value of quantitative rather than the merely qualitative PgR data in the group of patients with PgR analysis performed > 6 months prior to the start of treatment. Our data clearly show that PgR levels > 100 fmol/mg protein are an excellent indicator of hormonal responsiveness with an expected response rate of more than 80%. Furthermore, the quantitative PgR data proves to be superior to the quantitative ER data as illustrated by our finding that given a PgR level > 100 fmol/mg protein 85% of the patients show an objective remission, irrespective of the ER levels.

Several reports, including ours, indicate that about 40–50% of the initially PgR+ve tumors become PgR−ve in analyses of subsequent biopsies whereas about 15% show the reverse change in PgR status [6–9]. In view of this considerable inconsistency of the PgR status the present data on the predictive value of PgR is not too unexpected. For ER a suchlike high discordance rate has not been established [6, 7, 8, 13] indicating that the predictive value of ER will not be affected by the timing of the ER analysis as confirmed in this study. From the data on the quantitative PgR analysis we hypothesize that tumors with initially low PgR levels are more liable to become PgR negative in subsequent biopsies than the tumors with the higher PgR levels. In the study of Harland *et al.* [7] as well as in ours [8] the PgR levels in the tumors changing from positive to negative were generally lower than those in the tumors which remained PgR+ve.

Apart from the interval between the biopsy and the start of the endocrine treatment, other factors may have contributed to the outcome of this study. One might wonder whether the predictive value of the PgR status as assessed in metastatic tumor tissue differs from that obtained in the primaries. However, we did not find any difference in the frequencies of either primary tumors nor metastases as the source of tissue analysed between the several subgroups of patients.

Patients with visceral metastases are more likely to lack accessible tumor tissue for PgR analysis immediately prior to the start of the treatment and thus could have been over-represented in the group of patients with PgR analysis performed > 6 months prior to the start of the treatment. In that case lower response rates would have been expected merely because of the lower response rates to endocrine therapies in patients with visceral metastases. However, no such imbalance was noted in our study.

In conclusion, the clinical usefulness of PgR in the management of advanced breast cancer has to be reappraised in view of the findings presented in this study. The qualitative PgR status of ER+ve breast cancer tissue contributes significantly to the predictability of the outcome of the first endocrine treatment when PgR is analysed immediately prior to the start of such therapy. Whenever tumor tissue is inaccessible to perform a biopsy with PgR analysis, the quantitative rather than the qualitative PgR results of a former biopsy permit a better prediction of hormonal responsiveness than the quantitative ER data.

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