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E14. The prognostic and predictive value of the progesterone receptor in women with an oestrogen receptor positive breast cancer

P. Neven *, H.J. Huang, R. Vanspauwen, F. Amant, P. Berteloot, E. Van Limbergen, H. Wildiers, R. Paridaens, M.R. Christiaens, I. Vergote

Department of Gynaecological Oncology and Multidisciplinary Breast Center UZ KULeuven, Herestraat 49, 3000 Leuven, Belgium

1. Introduction

The oestrogen receptor (ER) is present in over 80% of women with breast cancer. The majority (80%) of ER-positive breast cancers are progesterone receptor (PR)-positive. In this extended abstract, we provide evidence regarding the current prognostic value of PR-expression in ER-positive breast cancer patients. We also show some of our own data in ER-positive breast cancers regarding tumour characteristics by PR-status. We note that an absent PR in ER-positive women predicts for nodal status only in women under the age of 50 years.

A significant proportion of women with an ER-positive breast cancer do not respond to endocrine therapy such as ovarian suppression, tamoxifen or aromatase inhibitors. The presence of PR in women with an ER-positive breast cancer supposes that oestrogens regulate tumour growth through an intact ER-pathway which may imply that endocrine therapy works better than when the PR is not expressed. Is PR of any additional value in predicting the patient's response to hormonal therapy in women with an ER-positive breast cancer?

2. PR: Independent prognostic marker in breast cancer?

Results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) and other large studies compared untreated women with an ER-negative tumour and those with an ER-positive breast cancer. Those with an ER-positive tumour have a longer disease-free survival (DFS) of approximately 10% at 5 years [1]. The same authors found that PR is a better predictor of response to hormonotherapy than ER. This is understandable because almost all women with a PR-positive tumour also express ER [2] which may imply that the ER-positive/PR-negative group is less sensitive to anti-oestrogens. The ER-positive/PR-negative phenotype is more likely to be seen for tumours with a high tumour grade and high proliferative activity. This group has an intermediate survival that is between the rate observed for women with a positive or negative expression of both the ER and PR, independent of the therapy received [3,4]. This implies there are, based on the joint ER/PR status, probably 3 prognostic groups that have a worsening outcome from ER+PR+, ER+PR- to ER-PR- (ER-PR+ patients only account for approximately 1–2% of the entire population). When other prognostic markers are considered, not all of the studies agree that PR has an independent prognostic value. This is because tumour grade and other markers for aggressive tumour behaviour, like S-phase fraction, outweigh a negative PR status as negative prognostic predictors in women with an ER-positive breast cancer [5,6,7]. Furthermore, longer follow-up studies show that the DFS and overall survival (OS) curves merge for the different prognostic groups of ERPR. Bardou and colleagues [8], in a recently published long-term follow-up study, reported on 2811 untreated women with an ER-positive, node-negative or node-positive breast cancer and concluded, from multivariate analyses, that the purely prognostic significance of PR among ER-positive patients for DFS and OS is extremely modest and probably only relevant in the short-term.

3. PR: An age-dependent prognostic effect?

In a series of 1473 primary breast cancers operated upon between 2000 and 2003, we assessed whether

*Corresponding author. Tel.: +32 16 34 46 35.
E-mail address: patrick.neven@uz.kuleuven.ac.be (P. Neven).

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patient and tumour characteristics in ER-positive breast cancers differ according to their PR-status. We excluded women with invasive lobular carcinomas, those receiving neoadjuvant therapy and those with an ER-negative breast cancer ($n = 470$). Women with an ER-positive/PR-negative breast cancer ($n = 239$) were older, more likely to have a high grade tumour and more likely to be HER-2/neu-overexpressors than those with PR expression. Women with PR-negative tumours had no differences in their tumour size or nodal status and the quantitative values of ER were not lower. However, our findings indicate that the prognostic significance of an absent PR may be age-related. In the small group of women under the age of 50 years with an ER-positive/PR-negative breast cancer (12.8%), an absent PR predicted for a positive lymph node status in low grade tumours ($P = 0.03$). In a multivariate analysis, PR remained an independent predictor for lymph node status in women under the age of 50 years, but with less power than for other predictors like tumour size and grade. A negative PR in an ER-positive breast cancer can be explained by lower circulating oestrogen levels that are no longer capable of inducing PR, but also by a defective ER-pathway. The age-dependent prognostic role of the PR can be explained by this mechanism. In younger women, the PR depends on ovarian oestrogens and an absent PR is more likely to reflect a defective oestrogen-responsive pathway than in older women where an absent PR is a natural variant because of low circulating oestrogens. We have no data on whether this loco-regional aggressiveness for an absent PR is reflected in a poorer outcome by age. A treatment independent prognostic effect for the PR will remain unknown because almost all women receive some form of adjuvant treatment.

4. PR: Is it predictive for response to hormonal therapy?

If an ER-positive breast cancer does not express PR, this may reflect that this tumour uses other pathways for growth than oestrogens alone. This may also implicate a lack of response to anti-oestrogens. Quantitative values of ER and PR have been reported to be predictive for a response to hormonal therapy; the higher the values, the better the response. However, few data are available on the effect of an absent PR as a predictor in women with an ER-positive breast cancer. In the metastatic setting, there is one large prospective study confirming a better overall response rate, a longer time-to-treatment failure and longer survival for tamoxifen users if the PR is also expressed. However, with longer follow-up, the effect of PR status disappears [9,10]. There are no data for a predictive role of PR status when using aromatase inhibitors in the metastatic setting. Whereas PR has only short-term prognostic value in women with an ER-positive breast cancer, recent evidence shows that PR is a long-term predictor for response to tamoxifen in the adjuvant setting. In 19 451 node-negative breast cancer patients in the Surveillance, Epidemiology and End-Results (SEER) database, Anderson and colleagues [11] examined breast cancer-specific survival according to the ER/PR status. In the short-term, DFS and OS curves between PR-positive and PR-negative women diverged on tamoxifen treatment. Women with an ER-positive/PR-positive breast cancer did better than those with an ER-positive/PR-negative tumour and, according to another database, PR was also predictive in the longer-term [8]. When ranking tumours from good to worse for ER+PR+ to ER+PR- to ER-PR+ to ER-PR-, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) observed relative improvements from tamoxifen treatment in early-stage breast cancer, but only for recurrence and not for survival [12]. This may be because PR was measured in many different laboratories. In the Bardou paper [8], all PR assays were performed at central laboratories with stringent quality control measures. Preliminary analysis suggests that the presence of PR may be the best available marker for an effect of anti-oestrogens when comparing tamoxifen with anastrazole in the adjuvant setting. In the Arimidex, tamoxifen, alone or in combination (ATAC) trial, women with an ER-positive/PR-negative breast cancer, after adjustment for nodal status, tumour size and grade, had clearly more benefit from anastrazole than from tamoxifen [13]. This indicates that the predictive role of PR is less important when using an aromatase inhibitor than tamoxifen at baseline. In women already on tamoxifen for 2 years, Ferno and colleagues [14] found that another 3 years of tamoxifen was not effective if the PR is absent; Coombs and colleagues [15] found that exemestane is better than tamoxifen in this situation, and also if the PR was expressed, as has been found for switching to anastrazole in a smaller study of high-risk women [16].

5. Conclusions

PR has a short-term prognostic value in the group of women with an ER-positive breast cancer. The age-related prognostic value of PR as a predictor for nodal status in women under the age of 50 years needs further exploration. The DFS and OS curves for patients grouped according to PR status diverge for patients on tamoxifen treatment. Aromatase inhibitors work better than tamoxifen in women with an ER-positive breast cancer when the PR is not expressed. In women on tamoxifen for 2 years, aromatase inhibitors work better in any PR-phenotype group at least for control of DFS.

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