Original Study

Survival Outcomes in Breast Cancer Patients With Low Estrogen/Progesterone Receptor Expression

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Abstract

The prognosis of tumors with low estrogen receptor (ER)/progesterone receptor (PgR) (ER/PgR 1%-10%) expression does not differ significantly from tumors with undetectable ER/PgR levels (ER/PgR < 1%). Further studies, probably prospective studies, are needed to identify the appropriate clinical approach in this subset of patients with low ER/PgR expression (ER/PgR 1%-10%), HER2-negative early breast cancer.

Introduction: The prognostic value of low estrogen and progesterone receptors expression (ER/PgR 1%-10%) in early breast cancer patients is still unclear. **Patients and Methods:** We retrospectively analyzed 1424 consecutive patients with HER2/*neu*-negative and low endocrine receptors expression early breast cancer, submitted to surgery at the European Institute of Oncology between January 1995 and December 2009. Patients were classified according to the percentage of ER/PgR expression using immunohistochemistry. Group 1 with ER/PgR $< 1\%$, and group 2 with ER/PgR 1% to 10%. **Results:** Group 1 (ER/PgR $< 1\%$) included 1300 patients, and group 2 (ER/PgR 1%-10%) 124 patients. Median follow-up time was 74 months (range, 3-192 months). The 5-year disease-free survival (DFS) rate was 74% (95% confidence interval [CI], 72%-77%) for group 1, and 79% (95% CI, 70%-86%) for group 2 ($P = .16$). The 5-year overall survival (OS) rate was 86% (95% CI, 84%-88%) in group 1 and 90% (95% CI, 83%-95%) in group 2 ($P = .13$). In patients without lymph node involvement, the 5-year OS rate was 92% (95% CI, 89.5%-93.6%) for group 1 and 98% (95% CI, 90.2%-99.8%) for group 2 ($P = .061$). One hundred ten patients received endocrine therapy with no significant effect on DFS ($P = .36$) and OS ($P = .30$). **Conclusion:** The ER/PgR 1%-10% group had a slight, but not statistically significant, better prognosis than the ER/PgR <1% group. Further studies are needed to identify the appropriate clinical approach in this subset of patients with low ER/PgR expression (ER/PgR 1%-10%), HER2-negative early breast cancer.

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Introduction

Hormone receptor-positive breast cancer, defined on the basis of the immunohistochemical expression of the estrogen receptor (ER) and progesterone receptor (PgR), constitutes approximately 60% of breast cancers arising in premenopausal women and 80% of those diagnosed after menopause.[1]

Estrogen receptor and PgR expression in early breast cancer patients are powerful predictors of response to adjuvant therapies.[2,3] It is recommended that endocrine receptors be measured in all primary breast cancer specimens,[4] and endocrine responsiveness is pivotal for selection of adjuvant systemic therapy.[5] It is also recognized that there are tumors with low endocrine responsiveness,

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in which receptor expression is quantitatively insufficient to indicate a substantial chance for response to endocrine therapies alone, which might suggest the need for chemotherapy.[5]

Recently, the endocrine responsiveness of tumors has been redefined on clinical, histopathology, and molecular bases.[6-8] In the past, the ER and PgR positivity and therefore eligibility for endocrine therapy[9-14] were considered in case of 10% or greater nuclear staining using immunohistochemistry (IHC). Recent international guidelines[15] recommended that tumors with any detectable ($\geq$ 1%) expression of ER and/or PgR using IHC are considered hormone receptor-positive. Therefore, an endocrine adjuvant treatment should be indicated in case of any ER staining in the tumor.[16] Up to now, the prognostic effect of low (ER/PgR 1%-10%) endocrine receptor expression in early breast cancer and the efficacy of adjuvant endocrine treatment in this patient population are still unclear. The aim of this retrospective study was to evaluate the prognostic and predictive effect of low expression of ER/PgR, in a large series of patients who had a homogeneous diagnostic and therapeutic environment for surgery, histopathology, and treatment assignment.

Patients and Methods

We extracted information from our prospectively collected institutional database on all consecutive breast cancer patients who received surgery at the European Institute of Oncology (EIO) between January 1995 and December 2009.

All patients were referred for interdisciplinary evaluation and systemic adjuvant treatment was recommended in accordance with the available St Gallen treatment guidelines.[5,16-18] Data on each patient's medical history, concurrent diseases, type of surgery, complete pathological evaluation, disease stage, and adjuvant treatment (radiotherapy and systemic chemo- and hormone therapies) were recorded and included in the analysis. Patients were followed up with physical examination every 6 months, annual mammography and breast ultrasound, blood tests every 6 to 12 months, and further evaluations only in case of symptoms. Whenever feasible the status of women missing the scheduled follow-up visits for more than 1 year, was obtained using telephone contact. All the included patients had pathological evaluation performed at the EIO. Tumor grade was assessed according to the criteria of Elston and Ellis,[19] based on the combined assessment of tubule formation, nuclear grade, and mitotic activity. Immunostaining for the localization of ER and PgR, HER2 and Ki-67 was performed on consecutive tissue sections. The following primary antibodies were used: 1 D5 monoclonal antibody (MAb) to ER (Dako, Glostrup, Denmark; 1/100 dilution), 1 A6 MAb to PgR (Dako, 1/800 dilution), MIB-1 MAb to the Ki-67 antigen (Dako, 1/100 dilution); the HER2 was evaluated with the A04851 polyclonal antiserum (Dako, 1/400 dilution) until 2006 and with the Herceptest kit (Dako) thereafter.[20] Only nuclear reactivity was taken into account for ER, PgR, and Ki-67 antigen, whereas only an intense and complete membrane staining in $>$ 10% of the tumor cells qualified for HER2 overexpression (3+). A fluorescence in situ hybridization analysis using the PathVysion HER2 DNA kit (Vysis; Abbott, Des Plaines, IL) was performed in cases with equivocal (2+) immunohistochemical results and gene amplification was defined as a HER2 to chromosome 17 centromere ratio $\geq$ 2. The results for ER, PgR, and Ki-67 were recorded as the percentage of immunoreactive cells observed among at least 2000 neoplastic cells. A threshold of 14% was settled for dividing cases with low ($<$ 14%) and high ($\geq$ 14%) Ki-67 labeling index (LI).[21] A tumor was considered triple-negative when both ER and PgR were negative or $<$ 1% and HER2 was not amplified or overexpressed. The tumor was regarded as positive for ER and PgR if $\geq$ 1% of the cells showed any definite nuclear staining.[22]

The study was approved by the Institutional Review Board.

Statistical Analysis

Differences in the distribution of subject characteristics between groups were evaluated using the χ^2 test.

The end points evaluated were disease-free survival (DFS) and overall survival (OS). DFS was determined as the length of time from the date of surgery to the date of any subsequent relapse (including ipsilateral breast recurrence, contralateral breast cancer, and appearance of a second primary cancer) or death, whichever occurred first. OS was determined as the length of time from the date of surgery until the date of death (from any cause). The DFS and OS functions were estimated using the Kaplan-Meier method. The log-rank test was used to assess differences between groups. The hazard ratio (HR) comparing ER/PgR $<$ 1% group vs. the ER/PgR 1%-10% group was estimated using a Cox proportional hazards multivariable model, controlled for age at diagnosis, number of positive lymph nodes, tumor size, Ki-67, and perivascular invasion. All analyses were carried out using SAS software version 8.2 (SAS Institute, Cary, NC). All reported P values are 2-sided. A P value of less than .05 was considered statistically significant.

Results

We identified 1424 consecutive patients with ER and PgR expression $\leq$ 10% and HER2/*neu*-negative early breast cancer who did not receive neoadjuvant chemotherapy. Group 1 (ER/PgR $<$ 1%) had a total of 1300 patients, group 2 (ER/PgR 1%-10%) had 124 patients.

Patient and clinical characteristics are shown in Table 1. The median age was 51 years. Compared with patients in group 2, patients in group 1 had a significantly greater prevalence of ductal carcinoma (87% vs. 81%; $P < .0001$), poorly differentiated (G3) (84% vs. 74%; $P = .008$), with a high ($\geq$ 14%) Ki-67 LI (94.4% vs. 87.9%; $P = .005$). Four percent of patients in group 1 received endocrine therapy in the adjuvant setting compared with 41% of patients in group 2 ($P < .0001$). Moreover, 53 patients (4%) in group 1 received chemoendocrine systemic adjuvant treatment vs. 46 patients (37%) in group 2 ($P < .0001$) (Table 2). The remaining main clinical-pathological characteristics including age, tumor size, nodal status, perivascular invasion, menopausal status, surgery, radiotherapy, and adjuvant chemotherapy were similar among the 2 groups (Tables 1 and 2).

Survival Outcomes

Median follow-up time was 74 months (range, 3-192 months). Survival outcomes (OS and DFS) according to ER/PgR values, estimated with their 95% confidence interval (CI) are listed in Table 3. We observed 186 (14%) deaths in group 1 and 11 (9%) in group 2. The 5-year OS rate was 86% (95% CI, 84%-88%)