Original article

Survival and clinicopathological characteristics of breast cancer patient according to different tumour subtypes as determined by hormone receptor and Her2 immunohistochemistry. A single institution survey spanning 1998 to 2010

A. García Fernández [a,*], N. Giménez [b,c], M. Fraile [d], S. González [e], C. Chabrera [f], M. Torras [a], C. González [g], A. Salas [g], I. Barco [a], L. Cirera [e], M.J. Cambra [h], E. Veloso [i], A. Pessarrodona [a]

[a] Breast Unit, Department of Gynecology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Spain
[b] Research Unit, Research Foundation Mútua Terrassa, University of Barcelona, Spain
[c] Laboratory of Toxicology, Universitat Autònoma de Barcelona, Barcelona, Spain
[d] Nuclear Medicine Department, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Spain
[e] Department of Oncology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Spain
[f] Department of Nursing, School of Health Science TecnoCampus Mataró-Maresme, Spain
[g] Department of Pathology, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Spain
[h] Department of Radiation Oncology, Hospital General de Catalunya, Spain
[i] Department of Surgery, University Hospital of Mútua Terrassa, Research Foundation Mútua Terrassa, University of Barcelona, Spain

ARTICLE INFO

ABSTRACT

As far as recent breast cancer molecular subtype classification is concerned, much work has dealt with clinical outcomes for triple negative and Her2 patients. Less is known about the course of patients in the remaining subtypes. Molecular classification based on immunohistochemistry is widely available and correlates well with genetic microarray assessment, but at a lower cost. The aim of our investigation was to correlate immunohistochemical subtypes of breast cancer with clinical characteristics and patient outcomes.

Since 1998, 1167 patients operated for 1191 invasive breast tumours were included in our database. Patients were regularly followed up until March 2010. Disease-free survival, overall mortality, and breast cancer-specific mortality at 5 years were calculated for the cohort.

72% of tumours were ER+PR±HER2− group, 13% triple negative (ER−PR−HER2−), 10% ER+PR±HER2+ group, and 5% Her2 (ER−PR−HER2+). Cancer-specific survival was 94.2% for the ER+PR+HER2− subtype, 84.8% for the Her2 subtype, 83.3% for the ER+PR−HER2− subtype, and 78.6% for triple negatives. Distant metastases prevalence ranged from 7% to 22% across subtypes, increasing stepwise from ER+PR+HER2−, ER+PR+HER2+, ER+PR−HER2−, ER+PR−HER2+, ER−PR−HER2+ through triple negative. Small, low-grade tumours with low axillary burden were more likely to belong to the ER+PR±HER2− group. Conversely, larger high-grade tumours with significant axillary burden were more likely to belong to Her2 or triple negative groups. ER+PR±HER2− group patients with negative PR receptors performed more like Her2 or triple negative than like the rest of ER+PR±HER2± groups patients.

Molecular classification of breast tumours based only on immunohistochemistry is quite useful on practical clinical grounds, as expected. ER+PR±HER2− group patients with negative PR receptors seem to be at high risk and deserve further consideration.

Introduction

Breast cancer is the most common cancer-related cause of death in women and the third most common tumour worldwide.[1] Breast cancer incidence and mortality may vary according to factors such as age, ethnicity, wealth and social status, as well as to tumour-related factors such as size, histological grade, and hormone receptor status.[2] Breast cancer is widely viewed as a multifactorial

* Corresponding author. OTC, Programa detección Precoz Cáncer de Mama, University Hospital of Mútua Terrassa, University of Barcelona, C/Sant Antoni 20, 08221 Terrassa, Barcelona, Spain. Tel.: +34 93 7365085; fax: +34 93 7365086.
E-mail address: agarcia@mutuaterrassa.es (A. García Fernández).

condition that consists of different and heterogeneous biological subtypes, each one of them associated with specific molecular and clinical characteristics that carry different prognostic and therapeutic implications.

The last few decades have witnessed major breakthroughs in the diagnosis and management of breast cancer patients. Population screening programs that allow early cancer detection on one hand and improvement in therapy on the other, have resulted in declining mortality rates and in better quality of life for those living with the disease.[3,4] On research grounds, however, much attention has been paid to newer molecular classifications of breast cancer,[5–14] which are based on genetic platforms or microarrays. Although very attractive for their prognostic power, these technologies are significantly limited from both availability and cost. On its own, immunohistochemical classification brings about important prognostic and therapeutic insights of breast cancer at a much lower cost. It is also widely available, and has been shown to correlate very well with intrinsic genetic expression microarray assessment as follows: ER±PR±HER2− and ER±PR± HER2+ as luminal, ER−PR−HER2+ as Her2, and ER−PR−HER2− as triple negative subtypes.[15]

The aim of our investigation was to correlate the different immunohistochemical subtypes of breast cancer, as well as the more classical prognostic factors, with patient disease-free survival, overall mortality, and breast cancer-specific mortality at 5 years.

Patients and method

Consecutive breast cancer patients referred to the Breast Unit of the University Hospital of Mútua Terrassa for surgical treatment of either primary or recurrent tumours were prospectively included in a database between January 1, 1998 and March 31, 2010. All patients had been referred either from the regional public health care system or from the Breast Cancer Screening Program of the Generalitat de Catalunya, West Valles Occidental section (Barcelona province). Patients with in situ carcinomas and those unfitted for surgery were excluded. The database of the Breast Unit included the following variables: age, tumour size, histologic type and grade (differentiation grade − G−, and histologic grade − HG), assessment of ER, PR, and Her2 status, as well as of nodal status, distant metastases occurrence, disease-free survival and mortality. This study was done in accordance with the Review Board and Ethics Committee of our centre. Written informed consent was always obtained before any invasive procedure as surgery.

All patients were treated according to the regularly updated protocol of the Breast Unit of the University Hospital of Mútua Terrassa, which follows both local and international guidelines. Chemotherapy regimes were based on anthracyclines and taxanes, and hormone therapy based on tamoxifen and aromatase inhibitors. From 2005 on, adjuvant trastuzumab was used for Her+ patients. Radiation therapy was performed at the nearby Hospital General de Catalunya using CT for bi-dimensional dosage planning until 2008. From then on, tri-dimensional planning was used, according to regularly updated protocols. In 2002, Sentinel Node (SN) biopsy was introduced for patients with tumours up to 3 cm in size and negative axilla, both clinically and sonographically.[16]

Hormone receptors were assessed by immunohistochemistry: DAKO Clone 1D5 was used for oestrogen receptors (ER), and DAKO Clone PgR 636 for progesterone receptors (PR). Assessment was based on the percentage of positive cell nuclei, independent of staining intensity. The positivity cut-off value was set at 5%. Her-2/neu protein over expression was determined by immunohistochemistry: DAKO HercepTest-TM,[15] and it was semi-quantitated based on staining of the cytoplasmic membrane rather than on cytoplasm itself. HercepTest was rated negative (0+ and 1+),

indeterminate (2+) or positive (3+). In cases of 2+, FISH or CISH techniques were used to evaluate gene amplification.

For the purpose of the present study, breast cancer was classified into eight subtypes based on hormone receptor oestrogens and progesterone and Her2 values as follows: ER+PR+HER2−; ER+PR−HER2−; ER−PR+HER2−; ER+PR+HER2+; ER+PR−HER2+; ER−PR+HER2+; ER−PR−HER2+; ER−PR−HER2−.

Given the different views on ER negativity significance when PR are positive,[17,18] those cases with ER− and PR+ were added to the ER+PR+ groups (14 cases in ER±PR+HER2−; and 2 cases in the ER±PR+HER2+ group). Therefore, the analysis is now restricted to only six subtypes: ER+PR+HER2−, ER+PR−HER2−, ER+PR+HER2+, ER+PR−HER2+, ER−PR−HER2+ (Her2) and ER−PR−HER2− (triple negative).

We studied variations of patient prognosis between groups as defined by the modified classification of Sorlie and Perou,[5] including the most prevalent subtypes within the ER+PR+HER2± groups. Other variables considered were age, tumour size, histologic type and grade, disease-free survival, all distant metastases, and specific visceral metastases, including liver, lung or brain, as well as mortality.

Mortality was considered per se (overall), and also as specific mortality from breast cancer, once other causes of death unrelated to breast cancer had been excluded. Mortality figures were derived from the mortality register of our own centre as well as from the database from the Catalan Public Health Care System. Survival was determined as a function of the total number of cases over the natural year count from the surgery date.

The actual minimum follow-up period was 12 months. 82% of patients were followed for 24 months, 70% for 36 months, 60% for 48 months, 52% for 60 months, 42% for 72 months, 34% for 84 months, 25% for 96 months, 20% for 108 months, and 14% for ten or more years.

Statistics

Time intervals were defined as time elapsed from the diagnosis of cancer to the last uneventful control or to event occurrence: local or distant recurrence or death. Qualitative variables were expressed as "n" and percentage, whereas quantitative variables were expressed as their mean value and standard deviation (SD). For comparison of qualitative variables the Chi-square test was used, while for comparison between mean values, the ANOVA was used. Statistical significance was set at p value <0.05, with a two-tail approach. The Kaplan−Meier and log-rank tests were used to calculate and compare survival rates. A multivariate analysis was used based on the Cox proportional hazard method, including those variables that were significant, as well as those with potential clinical impact. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Finally, 1167 patients suffering from 1191 invasive breast tumours that had been included in the breast cancer register of the University Hospital of Mútua Terrassa from January 1998 until March 2010 were entered into the study. Details of the exact number of analysed patients for each part of the study, as well as the exclusion causes are displayed in Table 1. Additionally, 188 patients that had been operated before HercepTest was available at our centre, but that indeed had hormone receptor assessment were also included. The mean patient age at diagnosis was 58 years. Most tumours were ductal carcinomas (91%), 50% were poorly differentiated, 58% were in the T1 size range, and 60% were node-negative. Baseline characteristics of study patients, including tumour subtypes are presented in Table 2. Out of the 1191 tumours, 72% were