The Breast 31 (2017) 46–50

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Improved survival in metastatic breast cancer 1985–2016

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ARTICLE INFO

Article history:
Received 7 October 2016
Accepted 10 October 2016
Available online 2 November 2016

Keywords:
Breast cancer
Metastatic
Survival
Prognosis

ABSTRACT

Purpose: In the last 25 years new treatment options in breast cancer have evolved. We wanted to determine whether the survival of; patients with metastatic breast cancer have improved during this period.
Methods: Patients consecutively diagnosed with disseminated breast cancer 1985–2014 in the County of Kalmar, Sweden, were identified and followed to 2016. Survival was calculated for each successive 5 year interval. Separate analyses were performed for pts with ER and/or PR and HER2 positive tumours resp.
Results: Median survival of the 784 patients increased successively from 13 to 33 months. Five year survival increased from 10 to 27%. Patients with high grade primary tumours had the shortest post recurrence survival time but their median survival increased significantly by time from 12 to 30 months, 3 year survival from 16 to 38% and 5 year from 5 to 20%. Median survival for patients with grade 2 tumours was 2 years and did not improve. Only 47 patients had grade 1 tumours and their median survival of 4 years did not change.
Median survival for HER2 positive patients treated before the introduction of trastuzumab in year 2000 was 14 months and after 2000 29 months, 5 year survival improved from 2 to 31%.
Conclusions: Survival in metastatic breast cancer improved 1985–2016. For the first time a significant increase in survival time for patients with metastasis from fast-growing grade 3 tumours was seen. The most striking improvement was achieved in the HER2 positive subset.

1. Introduction

Approximately one third of patients with primary breast cancer will eventually develop disseminated disease [1]. Disease-free interval is known to vary from months to decades. Mortality due to breast cancer occurs up to 40 years after primary diagnosis [2]. Systemic breast cancer is essentially incurable. Few per cent of patients diagnosed with distant metastasis die without signs of breast cancer [3]. The clinical course of patients with distant metastases is however highly variable. Some die within months after detection of dissemination but some live with a high quality of life for ten or more years.

In the last 25 years several new treatment options in breast cancer have evolved. The taxanes were introduced in the nineties, as were dose dense regimens of anthracyclines. Aromatase inhibitors came into use in the metastatic setting in 1997 and fulvestrant in 2005. The first immunologic treatment in breast cancer, trastuzumab, became available year 2000. We wanted to determine whether the survival of patients with metastatic breast cancer has improved during this period. Approximately 30–40% of patients with recurrences restricted to the preserved breast, ipsilateral chest wall or axillary nodes remain free of distant disease during an observation time of 7–10 years [4–6]. In the present study the outcomes of patients with truly disseminated disease was explored. Patients with loco regional recurrence or a new primary in the contra lateral breast without signs of distant metastasis were excluded from the investigation. Further, we wanted to assess predictors of disease development in metastatic breast cancer. Disease free interval [7,8], steroid receptor level [9], age [10,11], S-phase fraction [12,13], histological grade [5,7,12,14,15], histological type [16] and tumour HER2 expression [17] have been associated with survival after dissemination.

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http://dx.doi.org/10.1016/j.breast.2016.10.005
0960-9776/

2. Patients and methods

2.1. Patients

All patients with a diagnosis of disseminated breast cancer established between 1985 and 2014 in the county of Kalmar with 240 000 inhabitants were identified from the patient's registry. Patient and tumour data were retrieved from patient records and the pathology database. Patients with recurrences exclusively within the ipsilateral chest wall or mammary and axillary region were excluded as were tumours occurring in the contralateral breast. If distant metastases were diagnosed before or within 3 months from the diagnosis of the primary breast tumour it was classified as primary distant metastatic, de novo, disease.

To ensure the comparability of patients between time periods histological grading and receptor assessments were validated.

2.2. Pathology

Histological type and grade had been routinely assessed in the primary tumour and when possible in the metastases since 1985. Nottingham histological grade (NHG) was assessed according to the protocol of Elston/Ellis [18]. Validation of grading of the primary tumours was performed in 1999 and 2010 [19,20]. There was no significant change in the distribution of NHG 1, 2 and 3 in the primary tumours over the time periods. In 50 patients diagnosed with metastasis before 1990 and in approximately 1 patient each year thereafter it was not possible to grade the primary tumour. The primary tumour characteristics have been used in the investigation.

2.3. Hormone receptor determination

Before 2000 hormone receptor status were determined using 2 different cytosol assays. Until 1989 isoelectric focusing (IF) on polyacrylamide gel and thereafter an enzyme immunoassay (EIA) was used [21,22]. For ER, studies have shown that results with these techniques correlate well with those obtained using methods based on ultra-centrifugation, dextran-coated charcoal and immunohistochemistry [21–24]. The cytosol receptor values were normalized to DNA content as measured by Burton [25]. Cut-off values defined approximately 70% of the tumours as ER and/or PR positive.

Year 2000 and onwards tumour tissue was analysed for ER and PR status using immunohistochemistry. The fractions of ER and PR positive nuclei were determined and classified into four groups (0–10%, 11–50%, 51–75%, and >75%). Tumours with more than 10% positively staining nuclei were considered positive. The cytosol and IHC assays defined approximately the same proportion of tumours as positive [26] indicating the comparability of patients of different cohorts.

2.4. HER2 assessment

HER2 status was assessed in the primary tumours from 1996 and onwards using IHC and subsequently FISH. A polyclonal rabbit anti human antibody against the HER-2 protein was used (Dako A 0485). Only samples with distinct staining in more than 75% of the entire membrane and in more than 75% of the tumour cell were judged as overexpressed. FISH analysis was performed using the FDA-approved Path-Vysions HER-2 DNA ProbeKit. Signal ratios (HER2:CEP17) of $\geq$2 were classified as amplified.

2.5. Adjuvant treatments

In 1981 endocrine adjuvant therapy was introduced as postmenopausal patients with oestrogen receptor positive tumours were offered two years of adjuvant tamoxifen, which in 1995 was extended to five years. From 2004 postmenopausal women with high grade tumours or node positivity were offered aromatase inhibitors either for 5 years or for 3 years followed by 2 years of tamoxifen. From 1989 endocrine therapy with tamoxifen was used also for premenopausal patients with hormone receptor positive disease and in the early nineties 2 years of LHRH agonist treatment was added for this group of patients.

In 1981 also adjuvant chemotherapy was introduced when premenopausal patients with node positive disease received six months of CMF therapy. In the nineties adjuvant therapy with anthracycline containing regimens were introduced and used also for postmenopausal patient with node positive disease. From 2004 patients with high risk disease received adjuvant taxanes sequenced with anthracycline based therapy. From 2006 patients with HER2 amplified tumours were given trastuzumab for 1 year after chemotherapy. Only 11 of the patients with HER2 positive primary tumours had received trastuzumab in the adjuvant setting.

2.6. Data analysis and statistics

Survival curves were constructed and median survival in months from the date of diagnosis of distant metastasis was determined for each successive interval of five years 1985–2014 for the cohort as a whole and by grade. The percentage of patients surviving more than 2, 3, and 5 and 10 years after the first metastatic event was determined for each group.

In our hospitals the aromatase inhibitors came into use in the metastatic setting in 1997 and trastuzumab (Herceptin) in 2000. Fulvestrant (Faslodex) was introduced in 2005. Separate analyses were performed for patients with ER/PR positive and HER2 positive tumours, respectively, to determine whether the survival changed according to if distant disease was detected before or after the introduction of the new therapies. Significances were determined using Cox regression. Univariate survival distributions were estimated using the product limit method of Kaplan and Meier [27]. Death rates and tests of the statistical significance of relationship between study parameters and survival were computed using Cox's proportional hazards method [28]. Statistical analysis was computed using STATISTICA for Windows [29].

3. Results

Median disease-free interval (DFI) increased significantly over the time periods from 1, 8 to almost 6 years, p for trend <0.001.

The median survival of the 784 patients in the whole study population increased significantly from 13 months to 15, 16, 20, 23 and 33 respectively for each successive five-year period from 1985 to 2014, $p = 0.009$ (Fig. 1). Grade and hormone receptor status of the primary tumour were significantly correlated to survival after first metastatic event in the whole cohort of patients, $p < 0.001$ for both parameters.

3.1. Survival according to grade

For patients with grade 3 tumours ($N = 411$) the median survival improved gradually over time from 12 to 14, 15, 17, 17 and 30 months, for the six periods (Table 2, Fig. 2). The percentage of patients surviving more than three years improved from 16 to 38% and the five year survival increased from 3 to 17% (Table 1). The median survival for patients with grade 2 tumours ($N = 229$) was 23 months and did not change significantly. Only 47 patients had grade 1 tumours with a median survival of 39 months and no