European Journal of Cancer 83 (2017) 116–124

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Primary metastatic breast cancer in the era of targeted therapy – Prognostic impact and the role of breast tumour surgery

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Received 14 February 2017; received in revised form 11 April 2017; accepted 2 June 2017
Available online 20 July 2017

KEYWORDS
Breast cancer;
Primary metastatic disease;
Breast surgery;
Trastuzumab;
Bevacizumab

Abstract ***Background:*** Except for meeting the individual palliative need, the benefit of breast surgery in primary metastatic breast cancer (PMBC), also known as *de novo* metastatic breast cancer, on long-term outcomes remains controversial. Twenty-four hundred and one patients with metastatic breast cancer, enrolled between 2000 and 2011 in two prospective non-interventional studies on targeted therapy, were screened with respect to this question.
Methods: One study investigated trastuzumab therapy for human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer in addition to mainly first-line chemotherapy. The other observed bevacizumab added to chemotherapy as first-line treatment for mostly HER2-negative disease.
Results: Five-hundred and seventy (24%) patients presented with PMBC, and valid information on resection of the primary tumour was available for 568 women. Out of these, 426 (75%) underwent local resection. The latter group was characterised by less overall metastatic burden and a lower proportion of T4 tumours. No major differences were observed with respect to age, hormone receptor and HER2 status, visceral disease and performance status.

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http://dx.doi.org/10.1016/j.ejca.2017.06.002

Numerically, the surgery group showed a slightly favourable progression-free survival (PFS, medians: 13.6 versus 11.8 months; $P = 0.18$) and overall survival (OS, 34.1 versus 31.7; $P = 0.23$). However, in multivariable analysis, including all other univariably significant parameters, no trend for better outcome after surgery remained detectable, neither for PFS (hazard ratio 0.99; $P = 0.92$) nor for OS (0.95; $P = 0.71$).

Conclusions: Our findings suggest no major survival benefit for local resection in the overall PMBC population treated with modern targeted therapies. However, further analyses are warranted to define specific risk groups, which may benefit from surgical removal of the primary.

1. Introduction

In the developed countries, about 25% of the total population of breast cancer patients cannot be cured due to advanced stage or recurrent disease. Approximately 6% suffer from primary metastatic breast cancer (PMBC, also termed *de novo* metastatic cancer), i.e. test positive for metastatic disease synchronously, at the time of their first diagnosis of a mammary carcinoma [1–3]. Hence, approximately one out of four patients entering a palliative stage has stage IV disease (M1) disease at presentation. This incidence has remained unchanged during the last 25 years [4], while the prognosis of PMBC seems to have improved slightly, but steadily over time [2,4,5].

Although survival differences between PMBC and secondary metastatic breast cancer (SMBC) have been shown in retrospective studies, the prognostic relevance might have changed in the era of antibody treatment. Moreover, the impact of primary breast surgery remains controversial, in spite of a large number of studies on this topic [3,6,7]. We reanalysed two large prospective non-interventional studies conducted in Germany between 2000 and 2011 for patients with advanced/metastatic breast cancer (ABC) whose treatment for primary stage IV disease included antibody treatment [8–10]. The data from both projects were pooled in order to obtain a sufficiently large cohort for prognostic and subgroup analysis.

The main objectives of this pooled analysis are as follows: First, to characterise patients with PMBC and analyse the impact of this initial stage on long-term prognosis, compared to patients with SMBC. Second, to further characterise subgroups of PMBC patients with respect to the chosen local therapy approach, and analyse the impact of initial breast surgery on the long-term prognosis.

2. Patients and methods

2.1. Data sources and study design

All data were retrieved from two large prospective non-interventional studies, enrolling patients with ABC receiving antibody treatment:

- ML16684 (started in 2000): Observational study on trastuzumab (Herceptin®) in HER2-positive ABC, predominantly without palliative cytotoxic pre-treatment. In the majority of patients, trastuzumab was combined with chemotherapy (mostly a taxane), but monotherapy or combination of trastuzumab with antihormonal therapy was permitted as well.
- ML21165 (started in 2007): Observational study on bevacizumab (Avastin®) + paclitaxel as first-line cytotoxic therapy in predominantly HER2-negative ABC.

Treatment schedule concomitant to the respective antibody, diagnostics and frequency of follow-up visits were formulated at the discretion of the physician guided by the respective approved drug registration. Tumour response categories were assessed as best response achieved according to local standards, without strict requirements for subsequent remission confirmation. Additional details on the conduct of both observation studies were previously published [8–10]. For this analysis, data from patients presenting with PMBC at the initial cancer diagnosis were extracted and analysed, retrospectively. An unequivocal identification of the primary cM0/cM1 status was possible in 2401/2708 (89%) of all patients entering the observation studies (Fig. 1).

2.2. Statistical aspects

Progression-free survival (PFS) was defined as the time from the start of targeted therapy to disease progression or death; overall survival (OS) was defined as the time from the start of targeted therapy to death of any cause; PFS and OS were estimated by Kaplan–Meier product limit method. Univariable and multivariable analyses were performed using the log-rank test and Cox models [11], respectively. The latter included all prognostic factors with an associated $P < 0.1$ in the univariable analysis. Hazard ratios (HRs) were generally obtained from Cox models. Frequencies were compared with Fisher's exact test. Due to the retrospective nature of the study, all statistical analyses were considered exploratory, with $P \leq 0.05$ termed 'significant', and with no adjustments for multiplicity applied. All presented P values are two-sided. Data base lock was in July 2012 for patients in both studies.