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Original article

Palliative systemic therapy and overall survival of 1,395 patients with advanced breast cancer – Results from the prospective German TMK cohort study

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ABSTRACT

Data on treatment and outcome of advanced breast cancer in routine practice are rare, especially concerning recurrent disease, but important to complement the results from clinical trials and to improve the standard of care. We present data on choice of systemic first-line treatment, number of treatment lines, and survival of patients treated by medical oncologists in Germany.

1395 patients recruited by 124 sites at start of first-line therapy into the ongoing, prospective German clinical cohort study TMK (Tumour Registry Breast Cancer) between February 2007 and October 2015 were analysed.

The median OS was 33.8 months (95% CI 30.2–40.2) for HR-positive/HER2-negative, 38.2 months (95% CI 31.3–43.0) for HER2-positive and 16.8 months (95% CI 11.5–22.0) for triple negative breast cancer. Patients with triple negative tumours more often died before start of a third-line therapy than patients with HR-positive or HER2-positive tumours (44% vs. 25%). Use of taxane-based chemotherapies has increased since 2007, with 65% of all first-line chemotherapy-treatments containing taxanes in 2013–15 (60% HR-positive/HER2-negative, 75% HER2-positive, 56% triple negative). 52% of the patients with HR-positive/HER2-negative tumours received first-line endocrine therapy in 2013–15; when restricted to patients with only non-visceral metastases this percentage increased to 63%.

To our knowledge, this is the first cohort study showing systemic first-line therapy for all subtypes of advanced breast cancer. Overall survival in the TMK is comparable to that reported by clinical trials despite the inclusion of older and comorbid patients.

1. Introduction

Breast cancer is the most common type of cancer in women worldwide with an estimated 1.67 million new cases diagnosed in 2012, representing 25% of all cancers [1]. In Germany, about 70.000 women are newly diagnosed each year, with approximately 24% dying of the disease [2]. Advanced breast cancer constitutes 5–10% of all newly diagnosed breast cancer cases and depending on prognostic factors, the rate for relapse of initially localized disease ranges from 30 to 70% [3]. Despite ongoing research, advanced breast cancer generally remains incurable, associated with a median overall survival (OS) of 24–30 months [4,5]. Therefore, the

Abbreviations: ABC, advanced breast cancer; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; Bev, bevacizumab; C, cyclophosphamid; Cap, capecitabine; Car, carboplatin; CCI, Charlson Comorbidity index; CI, confidence interval; CTx, chemotherapy; D, docetaxel; DFI, disease-free interval; E/A, epirubicin/doxorubicin; eCRF, electronic Case Report Form; Eri, eribulin; ESMO, European Society for Medical Oncology; ET, endocrine therapy; Gem, gemcitabine; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Lap, lapatinib; MCR, Munich Chancer Registry; NCCN, National Comprehensive Cancer Network; OS, overall survival; P, paclitaxel; Per, pertuzumab; T-DM1, trastuzumab-emtansin; TMK, Tumour Registry Breast Cancer; Tra, trastuzumab; TT, targeted therapy; Vin, vinorelbine.

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main treatment goal is prolongation of survival and symptom palliation with maintenance or improvement of quality of life. Given the broad range of treatment regimens, the choice of first-line therapy needs to be based on tumour and patient related factors such as status of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2), tumour burden, prior neoadjuvant and adjuvant treatment, disease-free interval, comorbidities and patient preference. In the last 10 years, single-agent taxanes have been shown to be effective in terms of response rate and progression-free survival, yet considerable side-effects have to be taken into account [6–8]. For patients with HER2-positive tumours, the approval of new targeted agents, such as HER2-inhibitors, has greatly improved treatment options and survival [9]. While the current guidelines from AGO [10], ABC (ESO-ESMO) [5] and NCCN [11] point out these different treatment options, there is so far no recommendation of a specific first-line approach and the individual therapeutic decision is hence variable.

The variety of available treatment options and developments over the past decade raise the question how patients are treated in routine practice and how long actual survival outside of clinical trials is. However, such data are still rare.

Here, we present data from the cohort study TMK, which has been collecting data on patients treated for breast cancer in German routine care since 2007. We focus on advanced breast cancer, highlighting the choice and type of systemic therapy, number and sequence of treatment lines as well as overall survival (OS).

1.1. Patients and methods

1.1.1. Data source

The TMK is an ongoing, open, longitudinal, multicentre, observational, prospective cohort study. The study was approved by the responsible ethics committee and is registered at ClinicalTrials.gov (TMK registry, NCT01351584). More than 4500 patients have been recruited until 2016, half of them with early breast cancer, half with metastatic or inoperable locally advanced disease, here referred to as "advanced" breast cancer. The first patient was enrolled in February 2007. Eligible patients are women of $\geq$18 years of age with histologically confirmed breast cancer at the start of their systemic antineoplastic treatment in curative or palliative intention (endocrine therapy [ET], chemotherapy [CTx] or targeted therapy [TT]). Enrolment was restricted to patients who had signed informed consent no longer than six weeks after start of treatment to avoid immortal time bias, an overestimation of outcome data such as OS. In addition, data on tumour subtype had to be available.

At the time of this analysis 140 study sites were actively participating. Study sites were advised to recruit consecutively to minimise selection bias. At inclusion, patients' socio-demographics, prognostic factors (stage, grading, HR-status [estrogen and progesterone] and HER2-status), concomitant diseases and tumour characteristics (tumour location, histology) at primary diagnosis are collected. Comorbidity is assessed using the Charlson Comorbidity Index (CCI) [12]. Data on all neoadjuvant, adjuvant and current systemic treatments as well as radiotherapies and surgeries are documented, including start, end, dose, and number of cycles of all agents applied per line of treatment. Systemic therapies are documented by listing all agents separately and not as predefined regimens to allow for documentation of individual combinations.

Patients are treated according to physicians' choice and visit their physician on their individual schedule. No specifications are imposed to the physicians' assessment for treatment at any time. Patients can take part in a clinical trial or non-interventional study in addition to the registry. All patients are followed until death or up to five years from enrolment (or until loss to follow-up or withdrawal of consent). Follow-up is limited to 5 years due to funding reasons. During the follow-up period, data on all systemic antineoplastic treatments, on outcome and course of the disease are collected. Outcome parameters assessed as per centre standard include absence or presence and location of distant metastasis or local recurrence, date(s) of progression(s) and date of death by any cause.

Patients' data are transferred from medical records to a secure web-based electronic case report form (eCRF) by designated site staff and are updated after each follow-up visit, at any change in therapy or at least every six months. For quality assurance, data plausibility checks are performed and queries are generated automatically by the eCRF software. Manual checks on data completeness and plausibility as well as site monitoring are performed regularly to ensure the reliability of the data.

1.2. Sequential lines of treatment

The TMK collects information on sequential treatment according to the definition and documentation of "treatment line" by the participating physicians. For this analysis "palliative first-line treatment" is the first systemic treatment (ET or CTx) the patient received after diagnosis of metastatic breast cancer. Second-line treatment is the systemic treatment that was documented as subsequent treatment line. The therapeutic options ET or CTx shown in Fig. 6 include anti-HER2-targeted therapy (TT), if applicable and given in combination.

1.3. Statistical analysis

OS is defined as the interval between start of first-line therapy and date of death from any cause. Patients alive or lost to follow-up at data cut were censored at last contact. Kaplan-Meier estimates for OS were calculated using SAS for Windows Version 9.4 TS Level 1M2 with 95% confidence limits for the survival estimates. All analyses apart from OS were performed using IBM SPSS Statistics version 19.0.

2. Results

2.1. Cohort definition

Data cut-off for the present interim analysis was October 31, 2015. By then, 4507 patients with breast cancer had been recruited within the TMK, and 1584 patients had started their first-line palliative treatment for advanced or metastatic disease within 6 weeks of signing informed consent (Fig. 1). Of these 1584 patients recruited by 109 outpatient centres and 15 clinics for medical oncology located all over Germany, 1395 had documented data on the tumour subtype: 754 (54%) HR-positive/HER2-negative, 443 (32%) HER2-positive (with 301 [68%] of these HR-positive) and 198 (14%) triple negative tumours.

2.2. Patient and tumour characteristics

Table 1 presents demographic data and tumour characteristics of the 1395 patients included into this analysis. Median age at start of palliative first-line therapy was 63 years. Patients with triple negative tumours were diagnosed less often with synchronous metastases (22% M1) than patients with HR-positive/HER2-negative (30% M1) or HER2-positive tumours (32% M1). At start of palliative first-line therapy, patients with triple negative or HER2-positive tumours presented more often with visceral metastases (71%, 68%) compared to patients with HR-positive/HER2-negative tumours (59%). Depending on the subtype, 12–22% of the patients of the TMK cohort could be considered as ineligible for