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Original article

Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry

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ABSTRACT

Objectives: Improved progression-free survival is considered as treatment goal for patients with metastatic breast cancer (MBC) since it is assumed to delay or prevent deterioration of quality of life. Aim of our analysis was to examine the influence of disease progression on health-related quality of life (HRQoL).

Materials and methods: The PRAEGNANT study comprises a real-life registry for patients with MBC. HRQoL was assessed with the EORTC-QLQ-C30 Version 3.0 questionnaire at study entry and every 3 months thereafter. The primary endpoint was minimally important deterioration (MID) in global HRQoL score by ≥ five points between baseline and any follow-up assessment. A logistic regression model was

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Metastatic
Quality of life
QoL
Progression

built with MID (yes/no) at a follow-up timepoint as outcome variable and several covariates as predictors.

Results: In total, 329 patients were included in this analysis, with disease progression in 63 patients. Concerning the primary study aim, progression status predicted MID of global HRQoL status in addition to the other covariates. The adjusted odds ratio for the effect of progression status on MID was 2.22 (95% CI: 1.04 - 4.73). Comparisons of mean differences of QoL domains/scales yielded no differences.

Conclusions: We provide evidence that disease progression in patients with metastatic breast cancer in a real-world registry has a significant negative impact on HRQoL as measured by MID of HRQoL. This study emphasizes the relevance of avoiding progression and prolonging PFS to maintain QoL.

1. Introduction

In recent years, great advances have been made in treating advanced breast cancer. For the groups of patients with HER2-positive and with HER2-negative, hormone receptor-positive metastatic breast cancer, the introduction of pertuzumab and T-DM1 for HER2-positive disease [1,2] and mTOR inhibition [3] and recently for CDK4/6 inhibition [4–6] has greatly improved progression free survival [1–6] and for pertuzumab and T-DM1 also overall survival [1,7].

Overall survival is the most accepted and obvious endpoint in clinical trials. However, overall survival as primary endpoint of studies also presents some relevant limitations. On the one hand, very long follow-ups and large numbers of cases are required; on the other, changes in therapy behavior due to a long study period can introduce bias. Furthermore, after observation in a clinical trial, cross-over of the test substance into the control group after disease progression or to the numerous heterogeneous further therapies can influence outcome. Given these limitations, progression-free survival with the assumed therapy goal of delaying or preventing a deterioration of quality of life (QoL) is also considered an important patient-relevant objective [8].

Although these considerations seem obvious, discussion is ongoing about the best endpoint in clinical trials [8–12], also as part of the assessment process concerning decisions about drug approval and reimbursement. The endpoint, which is under debate to a considerable extent, is progression-free survival (PFS), defined as the time of study inclusion or randomization until disease progression or death. While most studies in metastatic breast cancer were designed with PFS as primary outcome variable [11] and while overall survival is considered the most reliable endpoint for cancer studies [13], PFS is the preferred endpoint among those based on tumor assessments. However “whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies” [13].

For most clinicians, preventing tumor progression with acceptable toxicities is a relevant endpoint since tumor progression is assumed to be associated with increased symptoms and psychological stress, impairing health-related quality of life (HRQoL). Symptoms, measured as patient-reported outcomes, are increasingly being added to the risk-benefit assessment of therapies. Longitudinal assessments of symptom scales and QoL assessments during treatment are usually part of clinical trials and are also increasingly implemented in cancer registries. Such analyses report HRQoL changes as well as time to HRQoL deterioration and improvement [14–16]. Randomization arms usually represent the basis for comparing two groups and it can only be assumed that progressions are the main influencing factors for HRQoL. However, analysis of HRQoL after progression is rarely documented in clinical trials and, consequently, data from patient cohorts of relevant size to examine this question are lacking. Aim of our analysis was, therefore, to examine the extent to which disease progression impacts QoL in a metastatic breast cancer registry. Specifically, we test the hypothesis that progression is associated with differences in global health status. Further exploratory study aims are the differences in other domains/scales of the EORTC-QLQ C30 questionnaire in this context.

2. Methods

2.1. The PRAEGNANT research network

The PRAEGNANT study (NCT02338167) [17] is a breast cancer registry that not only collects and analyzes data, but is also a real-time health-care tool for identifying patients who may be eligible for inclusion in clinical trials or for certain treatments. Furthermore, patients are asked to complete a set of QoL assessments at study entry and every 3 months thereafter. All patients provided written informed consent for the trial and this way for the authorization of using personal data within the PRAEGNANT network. The study was approved by all of the relevant ethics committees and institutional review boards.

2.2. Patient selection

Patients were required to have at least two QoL assessments. Patients with disease progression were required to have a QoL assessment at least 14 days, but not longer than 6 months before progression was documented. Furthermore, these patients were required to have a QoL assessment at least 14 days after the progression but not longer than 6 months thereafter (no patient died within this interval). This produced a group of 76 patients with an observation time ranging from 83 to 628 days. Therefore, patients without disease progression needed to have at least two QoL assessments that were between 80 and 630 days apart.

A total of 1744 patients were included in the PRAEGNANT study between July 2014 and March 2017. Patient selection is shown in Fig. 1.

2.3. Data collection

Clinical data were collected by trained and dedicated staff at the sites participating in the prospective PRAEGNANT study [17]. These data are monitored using automated plausibility checks and through random on-site field monitoring. Data that are routinely documented in the patient charts or electronic medical records are transcribed into electronic case report forms designed for that purpose. Additionally, data not routinely documented are collected prospectively using structured paper questionnaires once patients are registered in the study. These data comprise epidemiological data such as family history, cancer risk factors, QoL, nutrition and

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