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Original article

Treatment landscape of advanced breast cancer patients with hormone receptor positive HER2 negative tumors – Data from the German PRAEGNANT breast cancer registry

Andreas D. Hartkopf [a, 1], Jens Huober [b, 1], Bernhard Volz [c], Naiba Nabieva [c], Florin-Andrei Taran [a], Judith Schwitulla [c], Friedrich Overkamp [d], Hans-Christian Kolberg [e], Peyman Hadji [f], Hans Tesch [g], Lothar Häberle [c, h], Johannes Ettl [i], Michael P. Lux [c], Diana Lüftner [j], Markus Wallwiener [k], Volkmar Müller [l], Matthias W. Beckmann [c], Erik Belleville [m], Pauline Wimberger [n], Carsten Hielscher [o], Matthias Geberth [p], Nikos Fersis [q], Wolfgang Abenhardt [r], Christian Kurbacher [s], Rachel Wuerstlein [t], Christoph Thomssen [u], Michael Untch [v], Peter A. Fasching [c, *], Wolfgang Janni [b], Tanja N. Fehm [w], Diethelm Wallwiener [a], Sara Y. Brucker [a], Andreas Schneeweiss [k, x]

[a] Department of Obstetrics and Gynecology, University of Tuebingen, Tuebingen, Germany
[b] Department of Gynecology and Obstetrics, Ulm University Hospital, Ulm, Germany
[c] Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Germany
[d] Oncologianova GmbH, Recklinghausen, Germany
[e] Marienhospital Bottrop, Bottrop, Germany
[f] Department of Bone Oncology, Nordwest Hospital, Frankfurt, Germany
[g] Oncology Practice at Bethanien Hospital Frankfurt, Germany
[h] Biostatistics Unit, University Hospital Erlangen, Department of Gynecology and Obstetrics, Germany
[i] Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
[j] Charité University Hospital, Campus Benjamin Franklin, Department of Hematology, Oncology and Tumour Immunology, Berlin, Germany
[k] Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany
[l] Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany
[m] ClinSol GmbH & Co KG, Würzburg, Germany
[n] Department of Gynecology and Obstetrics, Technische Universität Dresden, Dresden, Germany
[o] gSUND Gynäkologie Kompetenzzentrum Stralsund, Stralsund, Germany
[p] Gynäkoonkologie Gemeinschaftspraxis, Praxisklinik am Rosengarten, Mannheim, Germany
[q] Department of Gynecology and Obstetrics, Klinik Hohe Warte, Bayreuth, Germany
[r] MVZ Onkologie, Onkologie im Elisenhof, München, Germany
[s] Department of Gynecology and Obstetrics, Medizinisches Zentrum Bonn Friedensplatz, Bonn, Germany
[t] Department of Gynecology and Obstetrics, Breast Center and CCC Munich, University Hospital Munich, Germany
[u] Department of Gynaecology, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
[v] Department of Gynecology and Obstetrics, Helios Clinics Berlin Buch, Berlin, Germany
[w] Department of Gynecology and Obstetrics, University Hospital Düsseldorf, Germany
[x] National Center for Tumor Diseases and Department of Gynecology and Obstetrics, Heidelberg University Hospital, Heidelberg, Germany

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ABSTRACT

Purpose: This study describes comprehensive data from a breast cancer registry concerning the use of endocrine treatment (ET) and chemotherapy in the first, second and higher therapy lines in hormone receptor (HR) positive, HER2 negative metastatic breast cancer (MBC).
Methods: The PRAEGNANT study is a real-time registry for patients with MBC. Therapies were categorized into the following categories: chemotherapy, aromatase inhibitor (AI), tamoxifen, fulvestrant, or everolimus plus ET and reported for first, second and third line or higher therapy use. Also treatment sequences for the first, second and third therapy line were analyzed.

* Corresponding author. Erlangen University Hospital, Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen EMN, Friedrich Alexander University of Erlangen–Nuremberg, Universitätsstrasse 21–23, 91054, Erlangen, Germany.
E-mail address: peter.fasching@uk-erlangen.de (P.A. Fasching).
[1] These authors contributed equally to this work.

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Results: This analysis includes 958 patients with HR positive, HER2 negative MBC. 42.7% were treated with a chemotherapy in the first therapy line compared to 45.9% receiving an ET. A total of 25.9% were treated with everolimus plus anti-hormone therapy in any therapy line. 34.1% were treated with fulvestrant as single agent therapy. Analyzing therapy sequences, the administration of three different chemotherapies in a row was the most frequently used pattern.
Conclusions: This analysis shows that across all three first therapy lines chemotherapy is a dominant therapy for HR positive, HER2 negative MBC patients. Education about the efficacy of ET might help to increase its use and decrease the possible burden of chemotherapy related toxicities.

1. Introduction

Metastatic breast cancer (MBC) has an extremely unfavourable prognosis and most patients die of their disease. In hormone receptor positive HER2 negative (HR + HER2-) cases, endocrine therapy (ET) should always be given before chemotherapy as current guidelines unanimously suggest [1–4], dependent on the individual patient's situation. Little is known about the adherence to these recommendations. Real-world evidence shows, that 22% to 38% [5–7] of patients receive a chemotherapy as first-line therapy of MBC. In some of the studies progression-free survival (PFS) and overall survival (OS) were compared between patients receiving chemotherapy and ET. One study did not find differences between patients receiving chemotherapy and ET [7]. Another study indicated, that patients treated with initial palliative chemotherapy had a worse outcome than patients receiving an initial ET [6].

Recently several novel therapeutics like everolimus [8], palbociclib and ribociclib [9–12], have shown they can overcome resistance mechanisms of endocrine therapies. Their addition to endocrine treatment has shown significant improvement of PFS for HR + HER2-. This might change the treatment patterns for MBC patients from chemotherapy to ET. Also, the timing and use of therapies like fulvestrant and everolimus + ET might have to be reconsidered in order to plan the best possible sequence of therapies for the individual patient. Certain combinations of ET are approved in combination with everolimus or palbociclib/ribociclib. Using those combinations partners in previous therapy lines might leave the treating physician with non-tested and non-approved combination partners or the choice not to prescribe the respective therapies.

Therefore, the objective of this study was to describe comprehensive evidence from a breast cancer registry concerning the use of tamoxifen, aromatase inhibitors (AIs), fulvestrant, everolimus and chemotherapy in the first, second and higher therapy lines, as well as the description of therapies given before the respective therapy line in HR + HER2- MBC patients.

1.1. Patients and methods

1.1.1. The PRAEGNANT research network

The PRAEGNANT study (Prospective Academic Translational Research Network for the Optimization of the Oncological Health Care Quality in the Adjuvant and Advanced/Metastatic Setting; NCT02338167, [13]) is an ongoing, prospective BC registry with a documentation similar to a clinical trial. Patients can be included at any timepoint during the course of their disease. All patients provided informed consent and the study was approved by the respective ethics committees.

A total of 1744 patients were registered between July 2014 and March 2017 at 47 study sites. Study sites were asked to recruit all advanced breast cancer patients in a consecutive way, ideally recruiting all advanced breast cancer patients who did not decline study participation. Of those, 91 patients had to be excluded because of missing HER2 status or unknown HR status. 103 patients with unknown date of first metastasis or birth year had to be excluded as well as 17 male patients. 132 patients had to be excluded because the therapy information in the metastatic setting was not available yet. Therefore for 1401 patients molecular subtypes and therapy information was available. Of those, 128 patients were triple negative and 315 were HER2+. The remaining 958 patients were HR + HER2-, (Fig. 1).

1.1.2. Data collection

The data were collected by trained staff and documents into an electronic case report form [13]. Therapy lines were documented in the given order, starting with the first therapy given for advanced breast cancer. Each therapy which was started thereafter was considered a higher therapy line regardless of the reason why the previous therapy was terminated. Data is monitored using automated plausibility checks and on-site monitoring. Data not usually documented as part of routine clinical work, are collected prospectively using structured paper questionnaires. This data comprises epidemiological data such as family history, cancer risk factors, quality of life, nutrition and lifestyle items and psychological health. Supplementary Table 1 provides an overview of the collected data.

1.1.3. Definition of hormone receptor, HER2 status, and grading

Data about estrogen receptor status, progesterone receptor status, HER2 status and grading were requested for documentation from each tumor, which had been biopsied. Therefore, there could be several sources (right breast, left breast, local recurrence, metastatic site). Biomarker status for ER, PR and HER2 were determined as follows: If a biomarker assessment of the metastatic site was available, this receptor status was taken for this analysis. If there was no information from metastases, the latest biomarker results from the primary tumor were taken. Additionally, all patients who were treated with an ET in the metastatic setting were assumed to be HR positive and all patients who were ever treated with an anti-HER2 therapy were assumed to be HER2 positive. There was no central review of biomarkers. Study protocol recommended to assess ER and PR status as positive if $\geq$ 1% were stained. A positive HER2 status required an IHC score of 3 + or a positive FISH/CISH.

1.1.4. Statistical considerations

Analysis and reporting of treatments are purely descriptive. Therapies are reported for the curative setting, the first-line and second-line metastatic setting. All therapies being given in third line therapy or beyond are reported cumulatively. Therapies were categorized into the following mutually exclusive categories: chemotherapy, AIs, tamoxifen, fulvestrant and everolimus plus endocrine therapy (EVE + ET).