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Human epidermal growth factor receptor 2 dual blockade with trastuzumab and pertuzumab in real life: Italian clinical practice versus the CLEOPATRA trial results

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ABSTRACT

Objectives: Given their inclusion and exclusion criteria, randomized clinical trials (RCT) might not include a population that truly mirrors real life (RL). This raises concerns about the applicability of RCT results in clinical practice. We evaluated the efficacy of anti-HER2 treatment with pertuzumab combined with trastuzumab and a taxane as first-line treatment for HER2-positive metastatic breast cancer in a RL setting, and compared the safety results obtained in our population versus the experimental cohort of the CLEOPATRA RCT, which led to the approval of this therapy.
Materials and methods: Patients treated with trastuzumab, pertuzumab and a taxane were enrolled in this retrospective study. We compared the tumor features and the patients' characteristics of the RL cohort to those of the CLEOPATRA cohort. We also compared the median progression-free survival (PFS) in the RL population versus specific patients' subgroups.
Results: RL patients were more frequently HR-positive, less likely to have visceral metastases ($P < .001$ for both) and had more frequently received (neo)adjuvant hormone therapy or trastuzumab than CLEOPATRA patients ($P = .004$ and $P < .001$, respectively). The median number of anti-HER2 cycles was 8 vs 24 and the median number of cycles was 7 vs 8 for docetaxel in the RL versus CLEOPATRA population, respectively. Adverse reactions of all grades were less frequent in RL. Median PFS was 27.8 months in the RL population and the treatment was equally effective in all patients' subgroups.

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Conclusion: This study provides compelling evidence that pertuzumab, trastuzumab and a taxane are effective and safe also in a clinical scenario.

1. Introduction

Breast cancer (BC) represents almost 15% of newly diagnosed cancers annually worldwide and of these, approximately 6–10% are initially metastatic and 20–30% will become metastatic [1]. Breast tumors are classified into five "intrinsic subtypes" (luminal A, luminal B, basal-like, claudin-low, and HER2-enriched) that differ in clinical behavior, prognosis and therapeutic options [2–4], because of their peculiar gene expression patterns [5]. The HER2-enriched subtype accounts for approximately 15–20% of all BC subtypes and, in clinical practice, it is generally characterized by the amplification and/or overexpression of the human epidermal growth factor receptor 2 (HER2) and its pathways [5,6]. Amplification and/or overexpression of HER2 is a marker of more aggressive tumor behavior and a bad prognosis if not treated [6–10].

The advent of anti-HER2 targeted therapies dramatically changed the natural history of this disease and the clinical outcome of patients with HER2-positive BC. Trastuzumab, a monoclonal antibody directed against the extracellular domain of HER2 was the first anti-HER2 agent approved in this setting and is now the standard of care for patients with early or metastatic HER2-positive BC. Recently, pertuzumab, a new HER2-binding antibody, was approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2012 and in 2013, respectively, for use in combination with trastuzumab and docetaxel as first-line treatment of patients with HER2-positive, locally advanced or metastatic breast cancer. Approval was based on the impressive results of the randomized phase III trial CLEOPATRA, namely, a progression-free survival (PFS) improvement of 6.1 months (18.5 vs 12.4 months, HR = 0.62, 95%CI: 0.51–0.75; $P < .001$) and an overall survival (OS) improvement of 15.7 months (56.5 vs 40.8 months, HR = 0.68, 95% CI: 0.56–0.84; $P < .001$) in patients in the pertuzumab arm [11–13]. However, the approval of new drugs is based on randomized clinical trials (RCTs) that are usually highly selective in terms of inclusion criteria, and might exclude patients with relatively frequent comorbidities (such as cardiac disorders) and specific metastatic sites (central nervous system metastases). Consequently, RCTs might not fully mirror "real-life" (RL) clinical practice patients - a finding that led to concerns about the full applicability of their results in the clinical setting [14–17].

Given the impressive results of pertuzumab and its increasing use in clinical practice, we conducted a retrospective analysis of 155 patients treated outside clinical trials in 8 Italian Institutes to evaluate the efficacy and safety profile of pertuzumab in RL patients, and compared our results to the results of the CLEOPATRA trial, when possible.

2. Materials and methods

2.1. Study design

This was an observational retrospective multicenter trial involving 8 Italian health care facilities in university hospitals and public hospitals. To be included in the trial patients had to have metastatic breast cancer, be HER2-positive according to ASCO/CAP guidelines [18] assessed on the primary lesion or on the metastatic site at tumor relapse, to have received trastuzumab and pertuzumab with a taxane as first-line treatment for metastatic disease and to have never been enrolled in interventional randomized clinical trials in a neo/adjuvant or metastatic setting. A total of 155 consecutive patients with HER2-positive metastatic BC who started first-line treatment with trastuzumab, pertuzumab and a taxane at the participant Institutions from August 2012 to December 2015 were enrolled. Table S1 shows the number of patients enrolled in each of the 8 Institutions. Docetaxel was administered at 75 or 100 mg/m^2 intravenously every three weeks, trastuzumab and pertuzumab were administered intravenously every three weeks at their standard dosage, while paclitaxel was administered weekly at a dosage of 80 or 90 mg/m^2.

The following data were retrieved from patients' charts at each participant institution and centrally collected in an anonymous database: demographic (age and baseline comorbidities), clinical (type of neo/adjuvant therapy received, i.e., trastuzumab, anthracyclines, taxanes and hormone therapy; type of taxane delivered with trastuzumab plus pertuzumab as first-line treatment for metastatic disease, overall duration of treatment, chemotherapy dose reductions, type and rates of adverse events of the taxane, pertuzumab and trastuzumab therapy), and tumor (metastatic sites at diagnosis, i.e., visceral, non-visceral, brain; hormone receptor [HR] status; HER2 assessment). Estrogen receptor (ER), progesterone receptor (PgR) and HER2/neu status on primary tumor after surgery or on tumor biopsy in case of *de novo* metastatic disease. Hormone receptor expression was considered positive in case of ER and/or PgR immunostaining greater than 1% of invasive cells. Estrogen receptor and PgR were analyzed as described elsewhere [19]. HER2 receptor status was evaluated by immunohistochemistry and expression level 3+ staining (DAKO Herceptest) was considered positive. In case of HER2 2+ staining or of equivocal HER2 1+ staining because of tumor heterogeneity, fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), or silver in situ hybridization (SISH) was performed to identify HER2 gene amplification.

Tumors were assessed every 3 months according to standard clinical practice, and tumor response, namely, stability or progression, was defined according to RECIST 1.1 criteria for measurable and not measurable disease [20] in the 8 centers participating in the study. Treatment toxicity was defined and graded according to CTCAE guidelines [21]. All RL patients underwent a basal cardiac evaluation with an echocardiogram to estimate the left ventricular ejection fraction (LVEF), and a specialist cardiovascular assessment, if needed, before starting first-line treatment with taxane, trastuzumab and pertuzumab. Echocardiography was performed every three months in all patients while on treatment with anti-HER2 agents, as per standard of care. Cardiac toxicity rates and time-to-recovery from cardiac toxicity was also recorded in our database.

All the information we retrieved for RL patients were also retrieved for patients enrolled in the CLEOPATRA study [11–13], if available, and our data were compared to those obtained in the CLEOPATRA trial. The study design was approved by the Ethics Committees of each participant center (IRB protocol number of the Coordinating Center: 176/15). Given the retrospective nature of the study, written informed consent was not required, according to Italian law.