The Breast 29 (2016) 153–159

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Toxicity of dual HER2-blockade with pertuzumab added to anthracycline versus non-anthracycline containing chemotherapy as neoadjuvant treatment in HER2-positive breast cancer: The TRAIN-2 study

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ARTICLE INFO

Article history:
Received 25 May 2016
Received in revised form
12 July 2016
Accepted 13 July 2016
Available online 5 August 2016

Keywords:
Breast cancer
Toxicity
Human epidermal growth factor 2
Neoadjuvant treatment
Trastuzumab
Pertuzumab

ABSTRACT

Background: The addition of pertuzumab to neoadjuvant trastuzumab-based chemotherapy improves pathologic complete response rates in HER2-positive breast cancer. However, increased toxicity has been reported with the addition of pertuzumab, and this may differ between various chemotherapy backbone regimens. We evaluated toxicities of pertuzumab when added to either FEC-T (5-fluorouracil, epirubicin, cyclophosphamide, trastuzumab) or weekly paclitaxel, trastuzumab, carboplatin (PTC).
Methods: The TRAIN-2 study is a neoadjuvant randomized controlled trial in stage II and III HER2-positive breast cancer (NCT01996267). Patients are randomly assigned to receive either three cycles of FEC-T plus pertuzumab or three cycles of PTC plus pertuzumab, followed by six cycles of PTC plus pertuzumab in both arms. Toxicities are described per treatment arm according to the Common Toxicity Criteria for Adverse Events version 4.03.
Results: This analysis includes 110 patients balanced over both treatment arms. Neutropenia was the most common hematologic toxicity, with grade 3–4 occurring in 53% in the FEC-T-arm and in 51% in the PTC-arm. Febrile neutropenia occurred in 9% in the FEC-T arm and did not occur in the PTC-arm. Secondary G-CSF prophylaxis was used in 35–40% of patients. Asymptomatic ejection fraction decrease grade 2 was observed in 24% in the FEC-T-arm and 11% in the PTC-arm. The most common grade 3–4 non-hematologic toxicity was diarrhea (5% in the FEC-T-arm and 18% in the PTC-arm).
Conclusions: Pertuzumab in combination with FEC-T mostly causes neutropenia, and when added to PTC mostly causes diarrhea. Significant cardiac toxicity is rare with both regimens, and toxicity is overall well manageable.

Introduction

Trastuzumab-based (neo)adjuvant chemotherapy is the standard of care for patients with stage II and III human epidermal growth factor receptor 2 (HER2) positive breast cancer [1]. The addition of pertuzumab to trastuzumab-based chemotherapy almost doubles the pathologic complete response (pCR) rate (from 22% to 39%) and has recently been registered for use in the neoadjuvant setting [1,2]. However, important toxicity has been reported as well, which may differ between various chemotherapy regimens. Thus, the optimal chemotherapy backbone for

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http://dx.doi.org/10.1016/j.breast.2016.07.017
0960-9776/

dual HER2-blockade is unknown, both from an efficacy and from a toxicity point-of-view. In particular, it is uncertain whether anthracyclines and cyclophosphamide should be part of the optimal chemotherapy regimen. Anthracyclines and cyclophosphamide are associated with severe long-term toxicities including cardiotoxicity, secondary malignancies, and infertility [3–5]. Therefore, regimens without these two agents might be preferable if the same efficacy can be achieved [3,6]. In the TRAIN-study we evaluated a trastuzumab-containing regimen with weekly paclitaxel and carboplatin and this regimen showed a promising high pCR rate (*van Ramshorst* et al. *submitted)*, within the same range as observed with regimens including dual HER2-blockade [2,7]. Subsequently, the TRAIN-2 study was designed to compare the efficacy and safety of six cycles of weekly paclitaxel, carboplatin, trastuzumab plus pertuzumab preceded by three cycles of weekly paclitaxel, carboplatin, trastuzumab plus pertuzumab or three cycles of 5-fluorouracil, epirubicin, cyclophosphamide, trastuzumab plus pertuzumab. Here, we report the toxicity analyses of the first 110 patients treated in the TRAIN-2 study.

Methods

Study design and patients

The TRAIN-2 study is a randomized, open-label, multicenter trial designed to compare the efficacy and safety of dual HER2-blockade with trastuzumab plus pertuzumab in combination with anthracycline-containing combination chemotherapy versus a non-anthracycline chemotherapy regimen in newly diagnosed stage II and III HER2-positive breast cancer patients (NCT01996267). Eligible patients were 18 years or older, treatment-naïve, and had no history of prior malignancy. Other eligibility criteria included a WHO performance status 0–1, a baseline left ventricular ejection fraction (LVEF) of $\geq$50%, adequate liver, renal, and bone marrow function, and no current pregnancy or breastfeeding. All patients gave written informed consent. The medical ethics committee of the Netherlands Cancer Institute approved the study protocol and any modifications thereof. The primary endpoint of the study is the percentage pCR. Safety was a key secondary endpoint, defined as the percentage patients with grade $\geq$3 toxicity, and grade $\geq$2 for cardiotoxicity and neuropathy. Toxicities were recorded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. This pre-specified safety analysis was performed after the first 110 patients had completed neoadjuvant treatment and had undergone surgery, which comprises 25% of the total planned accrual (n = 437).

Treatment schedule

Patients were randomly assigned to receive three cycles of three-weekly paclitaxel (80 mg/m^2 day 1 and 8), trastuzumab (6 mg/kg, loading dose 8 mg/kg), carboplatin (AUC = 6 mg·min/ml) [PTC] plus pertuzumab (420 mg, loading dose 840 mg) or three cycles of three-weekly 5-fluoruoracil (500 mg/m^2), epirubicin (90 mg/m^2), cyclophosphamide (500 mg/m^2) and trastuzumab [FEC-T] plus pertuzumab, followed by six additional cycles of three-weekly PTC plus pertuzumab in both arms (Supplementary Fig. 1). Physical examination, hematologic and biochemical investigations, and toxicity evaluation were completed before every chemotherapy cycle. LVEF measurements were repeated every three months or more often if indicated. Criteria for dose adjustments are summarized in Table 1.

Surgery was performed within six weeks of last chemotherapy and pathologic response was evaluated according to Dutch national guidelines, with pCR defined as the absence of any residual invasive tumor cell in the breast and axilla. After surgery adjuvant trastuzumab was continued to complete one year of treatment. Further adjuvant treatment was applied according to local guidelines.

Statistical analysis

Descriptive statistics of baseline, treatment, and toxicity data are reported according to treatment arm. Differences in treatment intensity and toxicity between the arms were tested for significance using the Wilcoxon rank sum test for continuous variables and the two-sided Fisher's exact test for categorical variables. All statistical calculations were made using R (www.r-project.org) and statistical significance was defined as $p < 0.05$.

Results

Between December 2013 and November 2014, 110 patients were included. All patients were female and median age was 47 years (range 32–73). Sixty-three percent of patients had stage II disease, and 63% had a hormone-receptor positive tumor. Baseline characteristics are summarized in Table 2.

Treatment intensity

Eighty-two percent of patients in the FEC-T-arm received all nine courses of treatment compared with 80% in the PTC-arm (Supplementary Fig. 2 contains a consort flow diagram). Chemotherapy dose was reduced in five patients (9%) in each arm during the first three treatment courses. During the subsequent six courses at least one dose reduction was implemented in 45% (25/55) of patients in the FEC-T-arm and in 56% (30/54) in the PTC-arm. The median number of received courses per drug and the administered cumulative dose as a percentage of the expected cumulative dose per drug are shown in Table 3.

Hematological adverse events

Grade 3–4 neutropenia occurred at a similar rate in both arms (53% vs 51%), although grade 4 neutropenia was more common with FEC-T (16% vs 4%; p = 0.06; Table 4). Febrile neutropenia was seen in five patients (9%) in the FEC-T-arm and in none in the PTC-arm (p = 0.06). G-CSF support was initiated following grade $\geq$3 neutropenia according to protocol in 40% of patients in the FEC-T-arm and in 35% of patients in the PTC-arm (p = 0.69), and prevented further grade $\geq$3 neutropenia in all but four patients. As described in Table 1, G-CSF support was not indicated if neutropenia occurred simultaneously with thrombocytopenia in the FEC-T arm.

Grade 3–4 thrombocytopenia was seen in ten patients in the FEC-T-arm and in seven in the PTC-arm, but was exclusively seen during the PTC cycles in both arms.

One patient was diagnosed with acute myeloid leukemia (AML) after three cycles FEC-T plus pertuzumab and two cycles PTC plus pertuzumab, which was considered possibly related to treatment, although the interval since start of chemotherapy was very short. However, cytogenetic analysis revealed a chromosome 16 inversion, which is described in association with topoisomerase II inhibitors like anthracyclines [8].

Cardiac toxicity

Cardiac toxicity was rare in both treatment arms. The lowest measured LVEF per patient ranged between 45% and 76% in the