Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial

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BACKGROUND

Although several randomised trials in patients with triple-negative breast cancer have shown that the addition of carboplatin, with or without poly(ADP-ribose) polymerase (PARP) inhibitors, to neoadjuvant chemotherapy increases the likelihood of achieving a pathological complete response, the use of these therapies in this setting has remained controversial. The BrighTNess trial was designed to assess the addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer.

METHODS

We did a phase 3, randomised, double-blind, placebo-controlled trial (BrighTNess) across 145 sites in 15 countries. Patients aged 18 years and older with previously untreated histologically or cytologically confirmed clinical stage II-III triple-negative breast cancer, who were candidates for potentially curative surgery and had an Eastern Cooperative Oncology Group performance status of 0 or 1, were randomly assigned (2:1:1) by an interactive response technology system via permuted blocks (block size of four) within strata to receive one of three segment 1 regimens: paclitaxel (80 mg/m intravenously weekly for 12 doses) plus carboplatin (area under the curve 6 mg/mL per min, intravenously every 3 weeks, for four cycles) plus veliparib (50 mg orally, twice a day); paclitaxel plus carboplatin plus veliparib placebo (twice a day); or paclitaxel plus carboplatin placebo (every 3 weeks for four cycles) plus veliparib placebo. Following segment 1, all patients were assigned to segment 2 in which they received doxorubicin and cyclophosphamide every 2-3 weeks for four cycles. Randomisation for segment 1 was stratified by germline BRCA mutation status, nodal stage, and planned schedule of doxorubicin and cyclophosphamide administration. The primary endpoint was pathological complete response in breast and lymph nodes as determined by site pathologists following completion of neoadjuvant therapy. Efficacy analyses were done by intention to

treat and safety analyses included all patients who received at least one dose of study treatment. These are the first results of an ongoing clinical trial; the data cutoff for the analyses presented was Dec 8, 2016. This study is registered with ClinicalTrials.gov, number NCT02032277.

FINDINGS
Between April 4, 2014, and March 18, 2016, 634 patients were randomly assigned: 316 to paclitaxel plus carboplatin plus veliparib, 160 to paclitaxel plus carboplatin, and 158 to paclitaxel alone. The proportion of patients who achieved a pathological complete response was higher in the paclitaxel, carboplatin, and veliparib group than in patients receiving paclitaxel alone (168 [53%] of 316 patients vs 49 [31%] of 158, p<0·0001), but not compared with patients receiving paclitaxel plus carboplatin (92 [58%] of 160 patients, p=0·36). Grade 3 or 4 toxicities, and serious adverse events were more common in patients receiving carboplatin, whereas veliparib did not substantially increase toxicity. The most common grade 3 or 4 events overall were neutropenia (352 [56%] of 628 patients), anaemia (180 [29%]), and thrombocytopenia (75 [12%]) through complete treatment, and febrile neutropenia (88 [15%] of 601 patients) during segment 2. The most common serious adverse events were febrile neutropenia (80 [13%] of 628 patients) and anaemia (20 [3%]).

INTERPRETATION
Although the addition of veliparib and carboplatin to paclitaxel followed by doxorubicin and cyclophosphamide improved the proportion of patients with triple-negative breast cancer who achieved a pathological complete response, the addition of veliparib to carboplatin and paclitaxel did not. Increased toxicities with the addition of carboplatin (with or without veliparib) to paclitaxel were manageable and did not substantially affect treatment delivery of paclitaxel followed by doxorubicin and cyclophosphamide. Given the consistent results with previous studies, the addition of carboplatin appears to have a favourable risk to benefit profile and might be considered as a potential component of neoadjuvant chemotherapy for patients with high-risk, triple-negative breast cancer.

FUNDING
AbbVie.

Kantonsspital St.Gallen

type	journal paper/review (English)
date of publishing	28-02-2018
journal title	Lancet Oncol (19/4)
ISSN electronic	1474-5488
pages	497-509