Neoadjuvant docetaxel plus cisplatin versus docetaxel plus doxorubicin and cyclophosphamide in early-stage triple-negative breast cancer (HELEN-001): results from a multicenter, randomized controlled, open-label phase II trial

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Article

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Abstract

Background

Adding platinum to anthracycline- and taxane-based neoadjuvant chemotherapy has improved pathological complete response (pCR) and event-free survival(EFS) in patients with triple-negative breast cancer (TNBC). However, the efficacy for TNBC of combining taxane and platinum without anthracycline remains controversial.

Methods

The HELEN-001 trial was a randomized, phase 2 controlled, and open-label investigation carried out in China at 6 hospitals. Participants who were aged 18–70 years old, were histologically confirmed for TNBC clinical stage II–III, suitable for potentially curative surgery, and had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1 were selected for this trial. Participants were randomized into two equal groups; those who received docetaxel plus cisplatin (75 mg/m^2, respectively) and those who received docetaxel plus doxorubicin and cyclophosphamide (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2). These regimens were given every 3 weeks for 6 cycles. Randomization was stratified by tumor size and nodal status. The primary endpoint was the number of individuals achieving a pCR (ypT0/isN0). The trial was registered with chictr.org (number ChiCTR-1800019501).

Findings:

Between November, 2018, and June, 2022, 212 patients were selected (n = 106/treatment arm). The number of individuals who achieved pCR after docetaxel plus cisplatin treatment was 51.9%, and that of those who attained pCR after docetaxel plus doxorubicin and cyclophosphamide was 35.8% (P = 0.019). After median follow-up of 29 months[interquartile range (IQR), 21 to 41], 14 of 106 patients (13.2%) in the docetaxel plus cisplatin group and 18 of 106 patients (17.0%) in the docetaxel plus doxorubicin and cyclophosphamide group had event-free survival (EFS) events [95% confidence interval (CI) = 0.377 to 1.526, hazard ratio (HR) = 0.759, P = 0.492]. The incidence of grade 3 or 4 events was similar in both groups [57 (54%) vs. 51 (48%)]. No treatment-associated deaths were identified in both groups.

Interpretation:

In stage II to III TNBC, the docetaxel plus cisplatin regimen achieved higher pCR rates than docetaxel plus doxorubicin and cyclophosphamide, with a comparable toxicity profile. Consistent with literature, the taxane plus cisplatin regimen demonstrated a favorable risk-to-benefit profile and could serve as an optimal neoadjuvant chemotherapy option for patients with high-risk TNBC.

Introduction

The triple-negative breast cancer (TNBC) is a specific subtype that lacks estrogen and progesterone receptors and the expression of human epidermal growth factor receptor 2 (HER2).It represents 10–20% of all breast cancer cases and is associated with an increased risk of recurrence, poorer prognosis, and limited treatment options than other subtypes[1,2].

Currently, neoadjuvant chemotherapy is the standard treatment approach for early TNBC as it provides both local and systemic control, facilitates de-escalation of surgery in cases with good response, and allows an *in vivo* assessment of tumor chemo-sensitivity. Anthracycline- and taxane-based combinations are currently the most frequently used neoadjuvant chemotherapy regimens for TNBC. However, despite these regimens, only approximately one-third of stage II–III TNBC patients achieve a pathological complete response (pCR) at surgery, which is associated with improved survival[3,4].

Several randomized trials have reported that adding platinum to anthracycline- and taxane-based chemotherapy substantially enhanced pCR rates of patients with TNBC. However, these regimens were associated with increased adverse events[5–7].

On the hand, cisplatin-based regimens without anthracyclines have demonstrated efficacy in advanced TNBC[8,9]. In the neoadjuvant setting for locally advanced TNBC, cisplatin has shown superior efficacy to carboplatin, leading to more patients achieving a pCR and significantly improved overall survival[10].

As a result,taxane plus platinum without anthracycline regimen is the new emerging alternative for treating TNBC.It offers a slightly different toxicity profile, and might be more effective in specific populations[11]. However, the evidence comparing taxane plus platinum with anthracycline- and taxane-based chemotherapy regimens as neoadjuvant treatment for TNBC are limited. Therefore, the HELEN-001 trial was carried out to investigate the efficiency and safety of neoadjuvant docetaxel plus cisplatin compared to that of docetaxel plus doxorubicin and cyclophosphamide in patients with stage II-III TNBC. This trial aimed to provide valuable insights into the optimal treatment approach for TNBC and refine treatment strategies for this challenging disease.

Methods

Study design and participants

HELEN-001 is a multicenter, randomized, phase 2, open-label trial conducted in China at 6 hospitals.

Individuals aged 18–70 years old, who had previously untreated histologically confirmed clinical stage – (T1N1-3 or T2-4N0-3) TNBC, were suitable for surgery, with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had been shown to have appropriate hematologic, renal, hepatic, and cardiac function were selected for this trial. Cardiac function was assessed by echocardiogram.

Individuals with a history of other malignancies, who had previously received chemotherapy or radiotherapy, or who had contraindications to the study drugs were excluded from this study.

Breast cancer was considered as TNBC subtype if estrogen and progesterone receptors expression were < 10% and HER2 was also negative, evidenced by immunohistochemical (IHC) staining 0–1 + or if IHC 2 + and fluorescence in situ hybridization (FISH) assay revealed no amplification of the *HER2* gene. In this study, the levels of estrogen, progesterone, and HER2 were elucidated locally.

This investigation was authorized by the ethical board of each participating hospital and followed the Declaration of Helsinki (as revised in 2013). All the individuals were first informed about the study, and then their consent were acquired.

Randomization and masking

Selected participants were randomized into two equal groups, with one group receiving docetaxel plus cisplatin and those who were admitted with docetaxel plus doxorubicin and cyclophosphamide via an interactive response system using permuted blocks (block size = 4) within strata. Randomization was carried out at the Henan Cancer Hospital and stratified by T stage (T1 to T2 vs. T3 to T4) and nodal status (N0 :node negative or suspicious imaging with negative biopsy vs. N+:node positive confirmed by biopsy).

Neither the patients nor the investigators were blinded to the assigned treatment.

Procedures

The treatments administered included docetaxel plus cisplatin (docetaxel 75 mg/m² on day 1; cisplatin 25 mg/m² on day 1 to day 3) or docetaxel plus doxorubicin and cyclophosphamide (doxorubicin 50 mg/m² on day 1; cyclophosphamide 500 mg/m² on day 1; docetaxel 75 mg/m² on day 2). A total of 6 cycles of these neoadjuvant treatments were given every 3 weeks. Pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) was allowed at the treating physician's discretion. To prevent cisplatin-mediated toxic renal effects, 12 hours of hydration treatment was given before and 24 hours after the docetaxel plus cisplatin regimen. In both treatment groups, dexamethasone and the receptor antagonists of NK-1 and 5-HT3 were given as antiemetic measures to prevent acute or delayed vomiting and nausea. Furthermore, standard premedications were also administered with dexamethasone to prevent docetaxel-induced hypersensitivity reactions.

After 2–6 weeks of the last neoadjuvant regimen cycle, participants underwent definitive surgery (breast conservation or mastectomy with sentinel lymph-node evaluation or axillary dissection). If patients present with T3-T4 primary lesions or positive regional lymph nodes prior to or after neoadjuvant therapy or if they undergo breast-conserving surgery, radiotherapy should be administered. In participants with residual disease, capecitabine (1,000–1,250 mg/m^2) was administered twice daily for 14 days and cycled every 21 days for 6–8 cycles[12]. The neoadjuvant regimen was discontinued in individuals who indicated disease progression, recurrence, or unacceptable toxic effects.

Adverse events were observed at each treatment and follow-up visit, which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0[13]. The patients were followed-up every 3 months after randomization for the first 2 years, then every 6 months for 3–5 years, and annually after year 5, to assess their disease status and mortality outcome..

Outcomes

The primary endpoint was the pCR rate, described as the absence of residual invasive carcinoma in both the axillary lymph nodes and breast on surgical histology.

Secondary endpoints included objective response rate (ORR), that is, the number of patients who achieved a partial or complete response based on Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria[14], rate of breast-conserving surgery, adverse events, and EFS. EFS was defined as the time from randomization to the date of pre-surgical disease progression, recurrence locally, regionally, or distantly, a second primary tumor, or death from any cause, whichever occurred first.

Statistical analysis

Assuming that the PCR rate for docetaxel plus doxorubicin and cyclophosphamide can reach 28%[15], docetaxel plus cisplatin has the potential to increase it by at least 17%, reaching 45%, with a $P < 0.05$ 1-sided significance level, 80% statistical power, and 10% dropout rate, the sample size was calculated as 106 participants/group.

SPSS 25.0 software (IBM Corp., Armonk, NY, USA) was utilized for statistical measurements. The pCR, breast-conserving surgery rates, and ORRs were compared using χ^2 tests. The incidence of adverse events was compared using χ^2 tests and Fisher's exact test. The Kaplan-Meier method was used to estimate the distributions of survival outcomes. Comparisons in survival rates were assessed by the log-rank test. Odds ratios (ORs), hazard ratios (HRs), and 95% confidence intervals (CIs) were assessed via the univariate logistic regression models and Cox proportional hazards models unless otherwise stated. In addition, we performed a test for the interaction between treatment and clinicopathological factors. All statistical measurements were 2-sided, and $P < 0.05$ was deemed significant.

Results

Between November, 2018, and June, 2022, 212 patients were enrolled in this study, with 106 patients in each treatment group (Fig. 1). In both cohorts, the baseline features were balanced, with a median age of 50 [interquartile range (IQR), 43 to 55] years at the time of enrolment (Table 1). Approximately 63% had histologically confirmed node-positive disease and 88% of participants had T1 or T2 tumors.

Table 1
Patient characteristics.

Characteristics	Docetaxel + cisplatin (n = 106)	Docetaxel + doxorubicin + cyclophosphamide (n = 106)
Age (years), median [IQR]	50 [43–55]	50 [43–55]
Age (years)		
≤ 50	54 (50.9)	54 (50.9)
> 50	52 (49.1)	52 (49.1)
T stage		
T1 to T2	93 (87.7)	94 (88.7)
T3 to T4	13 (12.3)	12 (11.3)
Nodal involvement		
Positive	68 (64.2)	66 (62.3)
Negative	38 (35.8)	40 (37.7)
ER and PR status		
ER and/or PR 1–9%	12 (11.3)	10 (9.4)
ER and PR < 1%	94 (88.7)	96 (90.6)
Ki-67		
≤ 50%	26 (24.5)	30 (28.3)
> 50%	80 (75.5)	76 (71.7)
gBRCA1/2 status		
Mutant	14 (13.2)	15 (14.2)
Wild-type	75 (70.8)	66 (62.3)
Missing	17 (16.0)	25 (23.6)

Data are median [IQR] or n (%). IQR, interquartile range; ER, estrogen receptor; PR, progesterone receptor.

Overall, 93 (43.8%) participants achieved pCR, and the number of patients who had a pCR was markedly higher in the docetaxel plus cisplatin cohort than that in the docetaxel plus doxorubicin and cyclophosphamide cohort [55 (51.9%) of 106 vs. 38 (35.8%) of 106, P = 0.019] cohort (Fig. 2). The subgroup analyses to compare the pCR rate of docetaxel plus cisplatin versus that of docetaxel plus doxorubicin and cyclophosphamide cohorts were consistent with this result (Fig. 3). For the subgroup analysis of 166 participants with known gBRCA1/2 status,the OR of docetaxel plus cisplatin versus that

of docetaxel plus doxorubicin and cyclophosphamide on pCR based on gBRCA1/2 status was 3.200 (95% CI = 0.621–16.494, P = 0.164) for those with mutation and 1.846 (95% CI = 0.932–3.657, P = 0.079) for those without this mutation, with interaction P = 0.544, suggesting that this difference could be because of the relatively few participants with BRCA variants (n = 25) (Fig. 3).

The results obtained for the tertiary endpoint minimal residual disease (residual cancer burden class 0 or 1), the pre-specified number of participants who indicated clinical breast tumor response, and the breast-conservation surgery rate between treatment groups were presented in Fig. 2.

At a median 29-month follow-up, 32 (15.1%) of 212 participants indicated EFS (Table 2). The Kaplan-Meier curves are presented in Fig. 4. Although no substantial difference in EFS was identified between the two cohorts (14 and 18 events were observed in the docetaxel plus cisplatin and docetaxel plus doxorubicin and cyclophosphamide cohorts, respectively, 3year-EFS = 87.3% vs. 83.9%, 95% CI = 0.377–1.526, HR = 0.759, P = 0.492), adequate efficacy analysis of docetaxel plus cisplatin on EFS will require prolonged follow-up and the occurrence of more events (Fig. 4A).

Table 2
First event-free survival event by treatment

End Point	Docetaxel + cisplatin(n = 106)	Docetaxel + doxorubicin+ cyclophosphamide (n = 106)
Patients included in analysis, No.	106	106
Event, No. (%)	14(13.2%)	18(17.0%)
Progression before surgery	2(1.9%)	3(2.8%)
Locoregional recurrence after surgery	4(3.8%)	6(5.7%)
Distant recurrence after surgery	7(6.6%)	8(7.5%)
Contralateral breast cancer	0(0.0%)	1(0.9%)
Death without prior EFS event	1(0.9%)	0(0.0%)
Stratified HR for TP v TAC (95% CI)	0.745(0.370–1.499)	
3-Year EFS, % (95% CI)	87.3(84.0 to 90.6)	83.9(80.3 to 87.5)
*HR adjusted by tumor stage and node status. EFS, event-free survival; HR, hazard ratio; TP, docetaxel plus cisplatin; TAC, docetaxel plus doxorubicin and cyclophosphamide; CI, confidence interval.		

Patients who achieved pCR had notably increased higher EFS than those with residual disease (3 events among 93 patients who achieved pCR vs. 29 events among 119 patients with residual disease; 3 year-EFS = 95.72% vs. 76.61%, 95% CI = 0.035–0.382, HR = 0.116, P < 0.001) (Fig. 4B).

Discontinuation was observed in 13 (12%) patients treated with docetaxel plus cisplatin (2 non-progression related adverse events, 1 withdrew consent, 2 progressive diseases, 8 other) and 16 (15%)

patients receiving docetaxel plus doxorubicin and cyclophosphamide (2 non-progression related adverse events, 1 withdrew consent, 3 progressive diseases, 10 other) (Fig. 1).

The dose reduction were 4(3.8%) of 106 patients in the docetaxel plus cisplatin group versus 5(4.7%) of 106 patients in the docetaxel plus doxorubicin and cyclophosphamide (P = 0.733). In the docetaxel plus cisplatin group, 1 patient (0.9%) of 106 required dose reduction of docetaxel and 3 patients (2.8%) required dose reductions of cisplatin.In the docetaxel plus doxorubicin and cyclophosphamide ,1 patient (0.9%) of 106 required dose reduction of docetaxel,2 patients (1.9%) required dose reductions of cisplatin and 2 patients(1.9%) required dose reductions of both.

Patients treated with docetaxel plus cisplatin and docetaxel plus doxorubicin and cyclophosphamide regimens had a comparable overall occurrence of grade 3 or 4 events [57 (54%) vs. 51 (48%), respectively]. The most common grade 3 or 4 overall events were nausea [31 (15%)], vomiting [20 (9%)], and diarrhea [20 (9%)]. The docetaxel plus cisplatin cohort indicated substantially higher grade 3 or 4 adverse events than the docetaxel plus doxorubicin and cyclophosphamide cohort for nausea [23 (22%) vs. 8 (8%)], vomiting [15 (14%) vs. 5 (5%)] and hypokalaemia [6 (6%) vs. 0 (0%)] (Table 3).

Table 3
Treatment-emergent adverse events

Events	Docetaxel plus cisplatin (n = 106)			Docetaxel plus doxorubicin and cyclophosphamide (n = 106)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Hematological, n [%]						
Leucopenia	22 [21]	3 [3]	2 [2]	13 [12]	4 [4]	4 [4]
Neutropenia	10 [9]	3 [3]	0 [0]	5 [5]	2 [2]	3 [3]
Febrile neutropenia	0 [0]	1 [1]	0 [0]	0 [0]	1 [1]	0 [0]
Anemia	68 [64]	4 [4]	0 [0]	60 [57]	3 [3]	0 [0]
Thrombocytopenia	8 [8]	2 [2]	2 [2]	7 [7]	1 [1]	3 [3]
Non-hematological, n [%]						
Nausea	54 [51]	23 [22]	0 [0]	65 [61]	8 [8]	0 [0]
Vomiting	55 [52]	15 [14]	0 [0]	33 [31]	5 [5]	0 [0]
Stomatitis	30 [28]	1 [1]	0 [0]	32 [30]	3 [3]	0 [0]
Constipation	45 [42]	0 [0]	0 [0]	40 [38]	1 [1]	0 [0]
Diarrhea	58 [55]	7 [7]	0 [0]	51 [48]	13 [12]	0 [0]
Abdominal pain	48 [45]	0 [0]	0 [0]	55 [52]	2 [2]	0 [0]
Myalgia	49 [46]	0 [0]	0 [0]	47 [44]	2 [2]	0 [0]
Arthralgia	40 [38]	0 [0]	0 [0]	44 [42]	2 [2]	0 [0]
Neuropathy	46 [43]	3 [3]	0 [0]	44 [42]	0 [0]	0 [0]
Dysgeusia	17 [16]	0 [0]	0 [0]	14 [13]	0 [0]	0 [0]
Pneumonitis	0 [0]	0 [0]	0 [0]	1 [1]	0 [0]	0 [0]
Laboratory-assessed items, n [%]						
Increased ALT	26 [25]	0 [0]	0 [0]	38 [36]	2 [2]	0 [0]
Increased AST	16 [15]	0 [0]	0 [0]	33 [31]	1 [1]	2 [2]
Increased bilirubin	10 [9]	0 [0]	0 [0]	2 [2]	0 [0]	0 [0]

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Events	Docetaxel plus cisplatin (n = 106)			Docetaxel plus doxorubicin and cyclophosphamide (n = 106)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Increased creatinine	18 [17]	0 [0]	0 [0]	2 [2]	1 [1]	0 [0]
Increased urea nitrogen	14 [13]	0 [0]	0 [0]	5 [5]	0 [0]	0 [0]
Increased uric acid	31 [29]	0 [0]	0 [0]	12 [11]	0 [0]	0 [0]
Hyponatremia	9 [8]	3 [3]	2 [2]	1 [1]	1 [1]	0 [0]
Hypokalemia	13 [12]	6 [6]	0 [0]	4 [4]	0 [0]	0 [0]
Hypercalcemia	11 [10]	0 [0]	0 [0]	9 [8]	0 [0]	0 [0]
Hypocalcemia	15 [14]	1 [1]	0 [0]	11 [10]	0 [0]	0 [0]
ALT, alanine aminotransferase; AST, aspartate aminotransferase.						

Furthermore, patients treated with docetaxel plus cisplatin had markedly fewer events of grade 1–4 increased alanine aminotransaminase (ALT) and aspartate aminotransferase (AST) but had more events of increased bilirubin, creatinine, urea nitrogen, uric acid, hyponatremia, and hypokalemia (Table 3). Serious drug-related adverse events were observed in 2 patients receiving docetaxel plus cisplatin (severe diarrhea and leucopenia) and 2 receiving docetaxel plus doxorubicin and cyclophosphamide (pneumonia and severe thrombocytopenia). There were no treatment-linked deaths in both groups.

Discussion

The HELEN-001 trial compared the efficacy of docetaxel plus cisplatin with that of docetaxel plus doxorubicin and cyclophosphamide as the neoadjuvant treatment for TNBC. The results indicated the docetaxel plus cisplatin regimen achieved higher pCR rates significantly than docetaxel plus doxorubicin and cyclophosphamide, with a manageable toxicity profile. To the best of our knowledge, this is the first trial to directly compare these two regimens in patients with TNBC.

The literature suggests that adding platinum to anthracycline- and taxane-based regimens enhances the pCR rate in patients with TNBC, although it was linked with high toxicity risk[5–7]. In contrast, neoadjuvant platinum-taxane regimens without anthracycline have demonstrated efficacy with a manageable toxicity profile in TNBC. For instance, the NeoSTOP trial indicated a pCR rate of 54% with the 6-cycle docetaxel plus carboplatin regimen but with a more favorable toxicity profile[16]. However, evidence comparing neoadjuvant platinum-taxane regimens with standard anthracycline-taxane regimens is few. The NeoCART trial reported a markedly increased pCR rate in patients treated with docetaxel plus carboplatin compared to those treated with epirubicin plus cyclophosphamide followed by docetaxel (61.4% vs. 38.6%, P = 0.044), with a pCR increase of 22.8%[17]. The data of this investigation are consistent with the

NeoCART trial, although the absolute increase in pCR in this trial (16.1%) was smaller, likely due to the higher tumor burden of participants, with 63% of patients having node-positive tumors, including those with N3 involvement. The strength of this trial is its original design, adequate sample size, and sufficient statistical power to detect pCR differences.

In our study, the pCR of the 6-cycle docetaxel plus cisplatin regimen was 51.9%, comparable to that of carboplatin, anthracycline, and taxane-based regimens in the Geparsixto, CALGB40603, and BrighTNess trials (53.2–57%)[5–7]. However, only 64–88% of patients in these trials completed all treatment cycles. In this trial, only 13 (12%) patients who received docetaxel plus cisplatin discontinued the treatment, and 2 discontinuations were due to severe toxicity.

Furthermore, cisplatin was used, partly due to the positive evidence from a few studies indicating its efficacy as a neoadjuvant treatment against TNBC[18–21]. Additionally, in another study involving 144 patients with TNBC,adding cisplatin to anthracycline- and taxane-based neoadjuvant chemotherapy increased pCR (36% vs. 21%, P = 0.076), improved progression-free (HR = 0.49, P = 0.007), and overall (HR = 0.40, P = 0.002) survival compared to adding carboplatin[10]. It is important to note that cisplatin and carboplatin have distinct spectrums of adverse reactions[22,23]. Therefore, it was postulated that combining docetaxel plus cisplatin could offer advantages over combining it with carboplatin regarding efficacy and hematological toxicity. Although the comparison of efficacy and safety of neoadjuvant regimens comprising cisplatin versus carboplatin was not assessed in this trial, the neoadjuvant regimen comprising cisplatin revealed a pCR rate similar to that of a carboplatin-containing regimen without increasing the occurrence of grade 3 or 4 adverse events compared to the anthracycline-taxane-based therapy. However, to compare the safety and efficacy of docetaxel plus cisplatin to that of docetaxel plus carboplatin, further prospective randomized trials are needed.

The dysregulated *BRCA* pathway is associated with TNBC[24,25]. In this study, 25 patients (11.8%) had *gBRCA1/2* mutations, consistent with the literature[26,27]. Platinum-based regimens have been shown to be effective in *gBRCA1/2* mutation carriers by a meta-analysis comparing between *gBRCA1/2* mutation individuals who received platinum-based treatment versus those who did not[28]. However, the exploratory analyses in this trial contradicted this. This might be because 1), the small sample size of gBRCA1/2 mutation carriers which restricted sufficient statistical measurement and differences analyses, and 2), non-*BRCA1/2* homologous recombination deficiency(HRD) carriers might have diluted and therefore, affected the results[27,29–31]. To confirm this, HRD detection for HELEN-001 study analysis is in progress.

The follow-up period of this trial was not long enough to depict prolonged EFS in the docetaxel plus cisplatin group than in the docetaxel plus doxorubicin and cyclophosphamide group. However, other investigations have indicated a sustained clinical benefit in TNBC patients who achieved pCR after neoadjuvant chemotherapy[3,6].

This trial had the following limitations: (I) the definition of TNBC might differ from the guidelines set by the College of American Pathologists, as the cutoff value of < 10% was applied for hormone receptor

negativity[32]. However, estrogen receptor 1–9% stained was considered equivocal, and low estrogen receptor-positive and -negative individuals had similar survival rates and may not be benefited from endocrine therapy[33]. (II) Docetaxel plus doxorubicin and cyclophosphamide was no longer a primary National Comprehensive Cancer Network guideline recommendation. According to the ECOG 1199 study findings, doxorubicin plus cyclophosphamide followed by a weekly paclitaxel regimen (AC-wP) may be better for TNBC patients. However, it was noteworthy that this trial was specifically focused on evaluating adjuvant therapy, and a direct comparison was required between the docetaxel plus doxorubicin and cyclophosphamide and AC-wP therapies to assess their effectiveness as neoadjuvant chemotherapy. (III) According to the KEYNOTE-522 study, adding pembrolizumab to neoadjuvant carboplatin plus weekly paclitaxel followed by anthracycline plus cyclophosphamide can improve pCR and EFS in TNBC[34–36], making it the optimal neoadjuvant treatment option for TNBC. However, at the time of this trial, pembrolizumab was not available in China. Based on the above preliminary results, another study HELEN-011 study (NCT05475678) has been designed to explore the efficacy of adding a programmed cell death protein 1 (PD-1) inhibitor to neoadjuvant docetaxel plus platinum chemotherapy in TNBC, which is currently underway. (IV) This trial was conducted in China, which may limit the generalizability of the results to other populations.

In summary, the HELEN-001 trial revealed that docetaxel plus cisplatin had a substantially increased pCR rate than docetaxel plus doxorubicin and cyclophosphamide against TNBC. Furthermore, the docetaxel plus cisplatin regimen also indicated a manageable incidence of treatment-related adverse events. Therefore, the taxane plus platinum regimen may serve as an alternative or even preferred neoadjuvant chemotherapy strategy for TNBC patients.

Declarations

Contributors

D Jiao, J Qiao,C Wang, Z Lu, L Li, M Yan,X Chen, Z Liu designed the study. D Jiao, J Qiao ,C Wang, Z Lu, L Li, M Yan, Y Feng, Y Zhou, M Deng, X Liu, M Ma, H Jia, X Chen, Z Liu developed the study methods.D Jiao, J Qiao, C Wang, X Sun, Z Lu, C Zhang, L Li, M Yan, Y Feng, Y Zhou, M Deng, X Liu, M Ma, H Jia, Q Xia, X Chen, Z Liu collected data. D Jiao, J Qiao and Q Xia had access to the raw data. D Jiao, J Qiao,C Wang, Z Lu, GH Lim, N Ishii, A Orlandi, F Hernanz and Z Liu analysed and interpreted the data.All authors contributed to manuscript writing,approved the final version, and are accountable for all aspects of the report. All authors contributed to drafting the manuscript, provided final approval to publish, and agree to be accountable for all aspects of the manuscript.

Declaration of interests

The authors have no conflicts of interest to declare.

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Figures

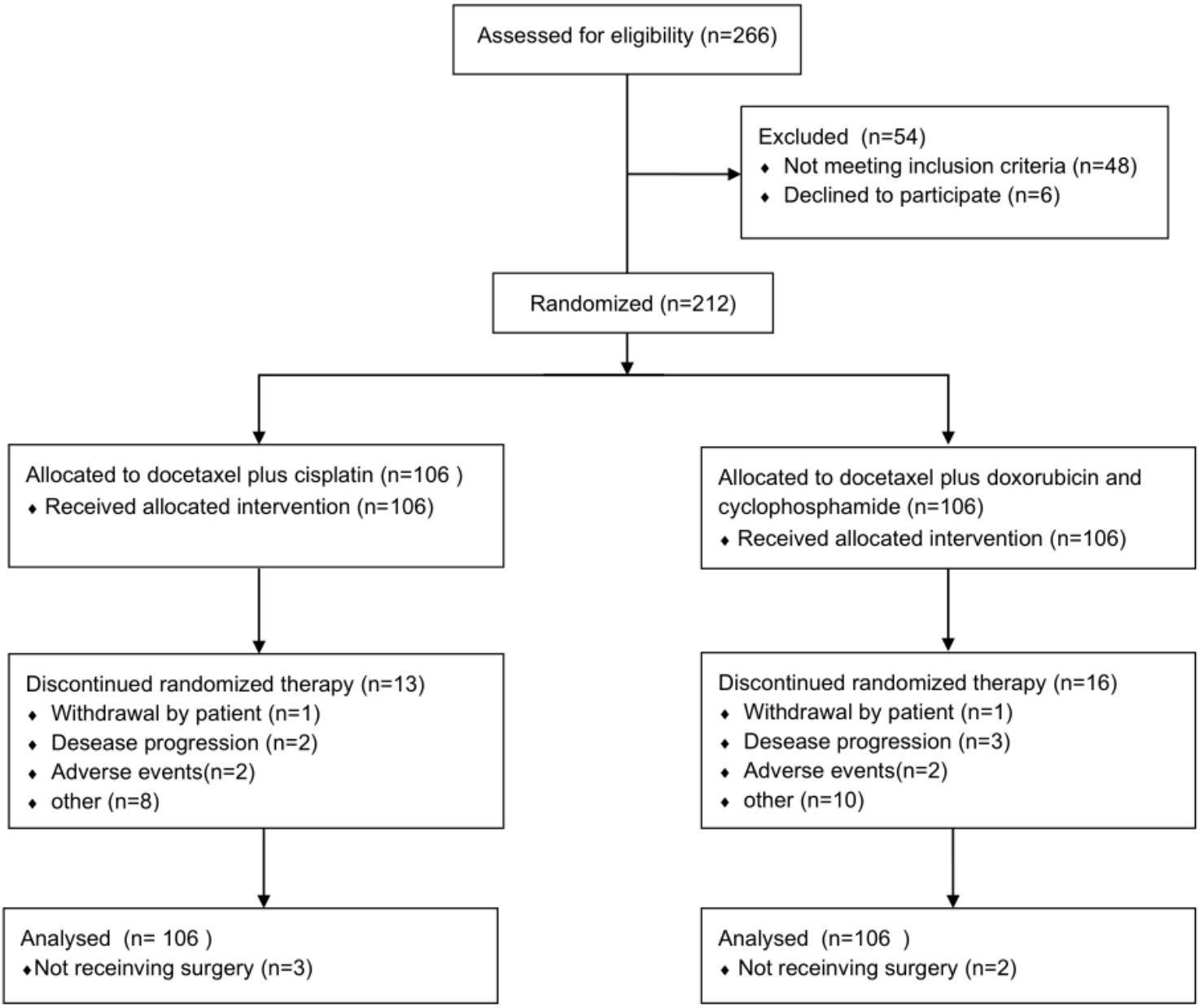

Figure 1

Consort diagram.

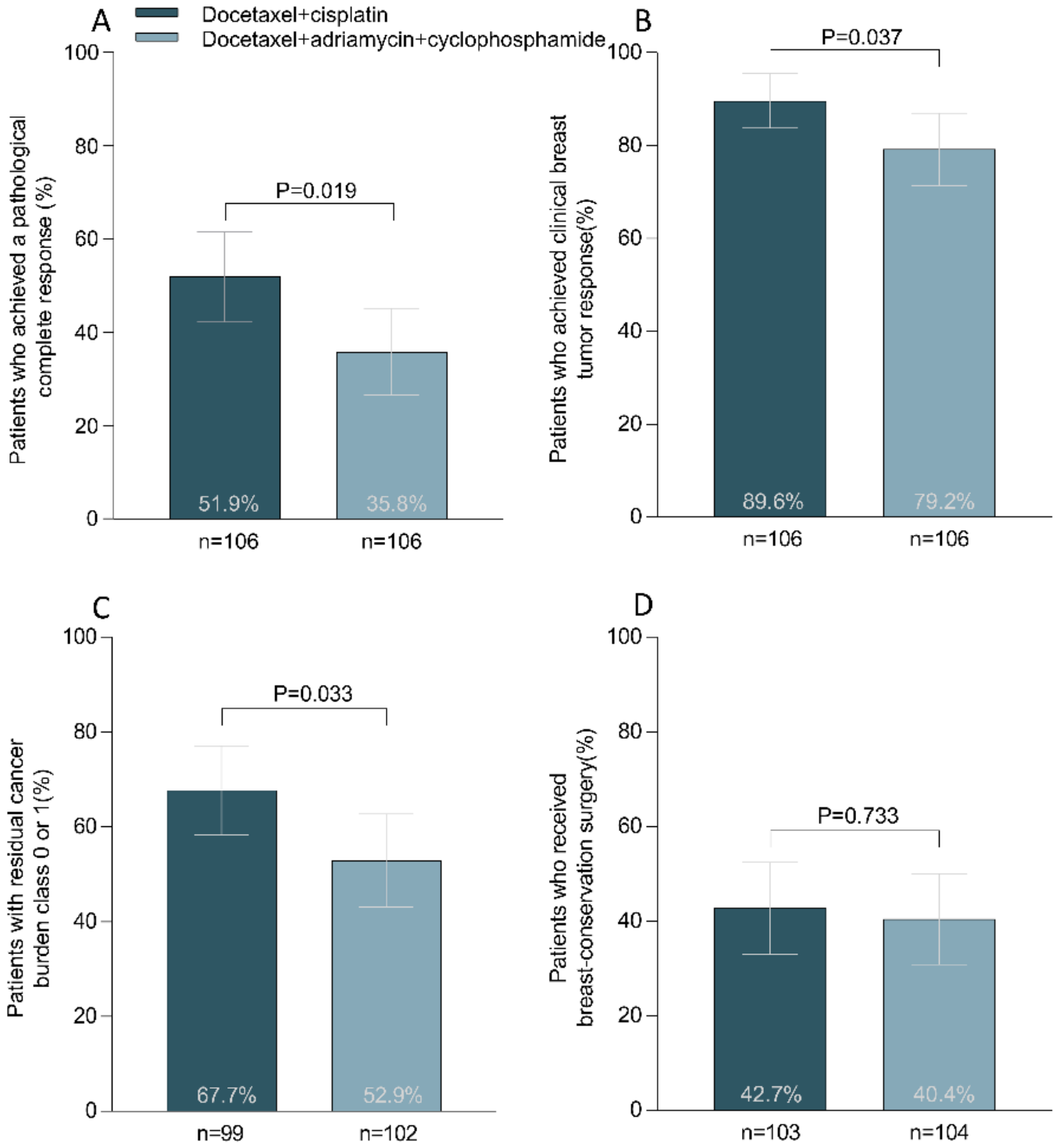

Figure 2

(A) Frequency of patients who achieved a pCR per treatment group (primary endpoint). (B) Frequency of patients who achieved a clinical breast tumor response per treatment group, assessed by serial MRI scans after completion of neoadjuvant treatment. (C) Frequency of patients who achieved a minimal residual disease (residual cancer burden class 0 or 1). (D) Frequency of patients who received breast-

conservation surgery. CI, confidence interval; MRI, magnetic resonance imaging; pCR, pathological complete response.

Error bars denote 95% CIs based on normal approximation. P values were calculated from the chi-square test.

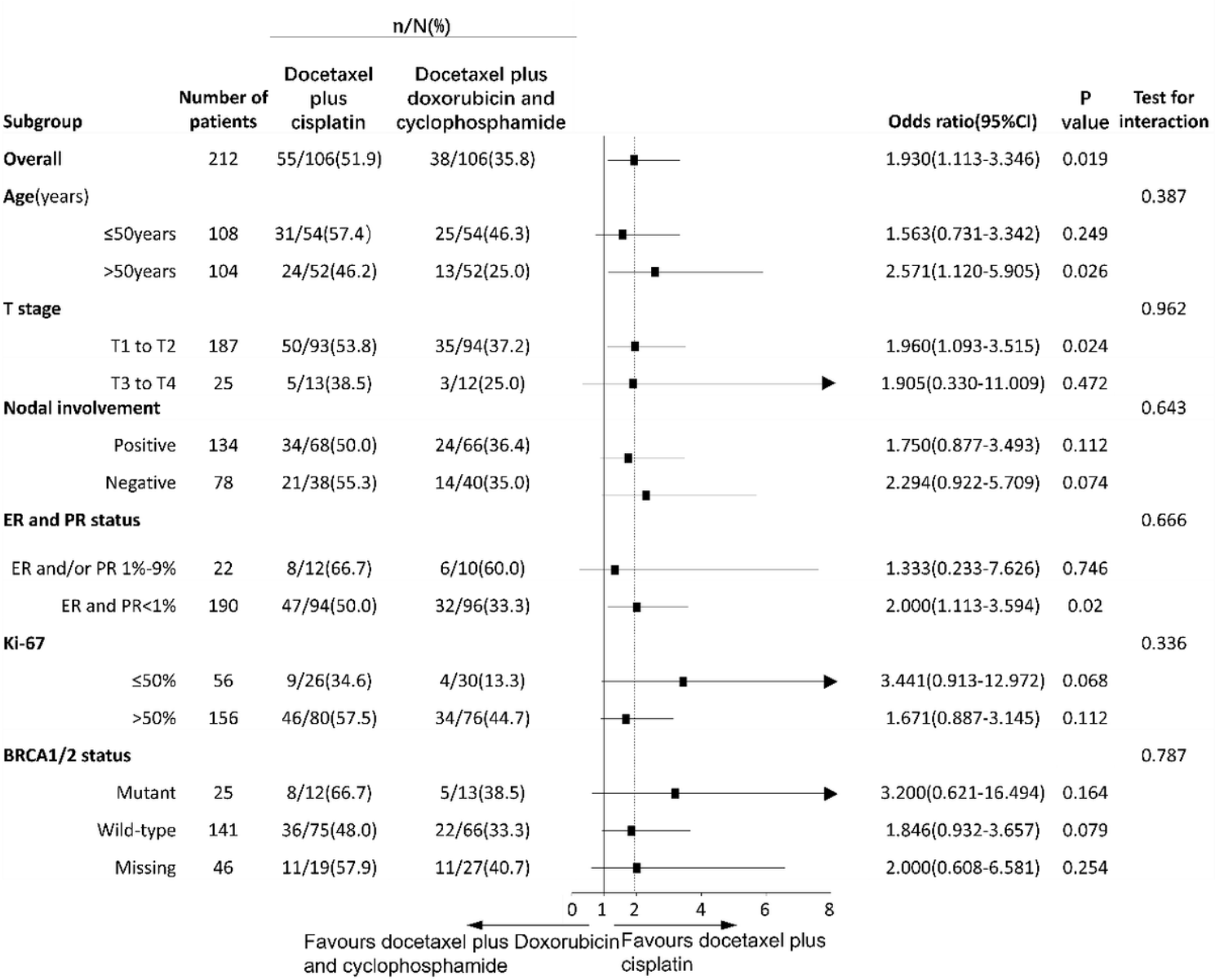

Figure 3

pCR by stratification variables. ER, estrogen receptor; PR, progesterone receptor; pCR, pathological complete response.

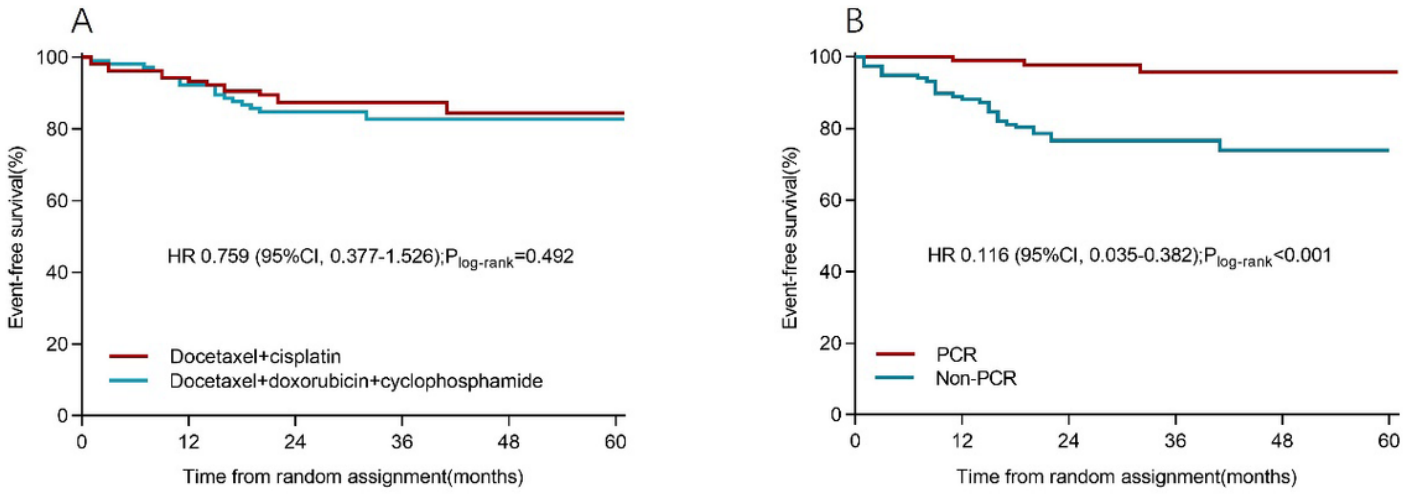

Figure 4

EFS according to treatment groups (A) and pCR (B) status. HR, hazard ratio; CI, confidence interval; TP, docetaxel plus cisplatin; TAC, docetaxel plus doxorubicin and cyclophosphamide; EFS, event-free survival; pCR, pathological complete response.