A randomised, controlled phase 2 study of neoadjuvant eribulin versus paclitaxel in women with operable breast cancer: The JONIE-3 study

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Abstract

Purpose: Neoadjuvant chemotherapy (NAC) is essential for surgical downstaging of early-stage breast cancer, but taxane administration is associated with neuropathy. We investigated whether eribulin induces less neuropathy than paclitaxel.

Methods: In this multicentre, randomised study (UMIN000012817), patients diagnosed with invasive breast cancer between December 2013 and April 2016 were randomly assigned to group E (eribulin followed by fluorouracil, epirubicin, and cyclophosphamide; FEC) or group P (paclitaxel followed by FEC). The primary endpoint was incidence of grade 1 or higher peripheral neuropathy according to the Common Terminology Criteria for Adverse Events (CTCAE). Secondary endpoints were pathological complete response (pCR), clinical response, breast-conserving surgery, adverse events, disease-free survival (DFS), and patient neurotoxicity questionnaire (PNQ) analysis.

Results: One hundred and eighteen cases were analysed for safety and 115 were evaluated for efficacy. Peripheral sensory neuropathy was significantly lower in group E after week 6, while peripheral motor neuropathy in group E was significantly lower at weeks 9, 12, and 15. pCR in groups E and P was 20.7% and 29.8% (P=0.289), respectively, and clinical response was 55.2% and 77.2% (P=0.017), respectively. Three-year DFS was 89.7% in group E and 86.0% in group P (P=0.561). Neutropenia was more frequent and more severe in group E. PNQ was evaluated for 4 years, and item 1 (sensory) was consistently lower in group E.

Conclusion: Neuropathy was significantly less frequent and less severe in patients who received eribulin compared with paclitaxel. Thus, eribulin could be a good alternative to paclitaxel in patients suffering severe neuropathy.

Plain Language Summary

The benefits of neoadjuvant treatment for early-stage breast cancer include tumour response assessment and prognosis estimation. However, standard neoadjuvant therapies for early breast cancer are associated with several adverse effects including debilitating neuropathy and neutropenia. We demonstrated that eribulin followed by an anthracycline was associated with less severe neuropathy than paclitaxel, offering an alternative treatment strategy for patients who cannot receive paclitaxel.

1. Introduction

Neoadjuvant chemotherapy (NAC) is actively administered to breast cancer patients, partly because response to NAC is a valuable indicator of the requirement for additional treatment [1, 2]. According to the Japanese Breast Cancer Registry, which is based on the National Clinical Database, 10% of 90,232 Japanese breast cancer patients without distant metastasis received NAC in 2017 [3].

The choice of chemotherapy regimen is dependent on the clinical status of the patient and their tumour subtype. NAC agents with proven efficacy include anthracyclines and taxanes such as paclitaxel, but they are associated with several side effects including neuropathy. Chemotherapy-induced peripheral neuropathy is a severe and dose-limiting adverse effect of neurotoxic chemotherapeutic agents and can lead to discontinuation of treatment in serious cases [4]. Paclitaxel targets microtubules, which are involved in neuronal function, and thus induces peripheral neuropathy in approximately 60–70% of patients administered paclitaxel for cancer treatment [5, 6]. Eribulin, a non-taxane microtubule dynamics inhibitor, was reported as having unique effects of vascular remodelling [7] [8] and suppression of epithelial–mesenchymal transition [9] and has shown improved overall survival in metastatic breast cancer patients and less frequent peripheral neuropathy [10, 11]. However, there are limited reports about the efficacy of eribulin for early breast cancer. In the HOPE study, promising antitumour activity of eribulin as NAC was observed in patients with triple-negative breast cancer who had received paclitaxel and doxorubicin [12]. The clinical benefit of eribulin-based treatment as NAC in triple-negative breast cancer was further compared with that of paclitaxel in another phase 2 study, demonstrating pCR rates of 65% and 45%, respectively [13].

To our knowledge, only two randomised trials compared eribulin with paclitaxel as NAC [14, 15], and eribulin was not as effective as paclitaxel. However, these trials did not focus on neuropathy, a possible advantage of eribulin. We performed a NAC study to determine if sequential administration of eribulin followed by anthracycline induced less peripheral sensory and motor neuropathy than paclitaxel followed by anthracycline and compared patient-reported neuropathy outcomes for more than 4 years. Our findings will enable clinicians to select alternative treatment strategies for early-stage breast cancer patients suffering from paclitaxel-induced neuropathy.

2. Materials And Methods

2.1. Study Design

This randomised, prospective, unblinded phase II study was conducted by Japan Organization Neoadjuvant Innovative Experts (JONIE), which was established to perform clinical trials and improve breast cancer treatment. This study compared eribulin with paclitaxel for 12 weeks, followed by four cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC). Registration was from 3 December 2013 to 13 April 2016, and the study was performed from 25 December 2013 to 31 December 2020. Patients were randomly assigned to receive eribulin (group E) or paclitaxel (group P) as the first agent by computer random-based allocation, and the registration number was sent from the data centre. The allocated treatment was not concealed from the physicians or the patients. Patients who received any other treatment were removed from the study. HER2+ patients were administered trastuzumab. Stratification factors were oestrogen receptor (ER), HER2, and menopausal status, and they were centralised at the data centre (Department of Medical Informatics of Niigata University Medical and Dental Hospital). HER status was assessed in accordance with the 2013 American Society of Clinical Oncology/College of American Pathologists clinical practice guidelines [16], while hormone receptor status was determined by the

presence of 1% or more oestrogen receptor-positive cells. The study protocol (UMIN000012817) was approved by the institutional review board of Tokyo Medical University on 25 December 2013 (approval number: SH2588) and subsequently by all participating institutions. Written informed consent was obtained from all participants prior to study inclusion.

2.2. Patient Eligibility

The inclusion criteria of this study were: stage II–IIIb hormone receptor-positive and HER2-negative breast cancer and stage Ic–IIIb triple-negative or HER2-positive breast cancer; Eastern Cooperative Oncology Group performance status of 0–1; aged over 20 years; and diagnosed with invasive breast cancer via core-needle biopsy before treatment. Exclusion criteria were: pregnancy; breastfeeding; or bilateral breast cancer (synchronous or asynchronous).

2.3. Treatment

Patients received either four cycles of eribulin 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle (group E) or weekly paclitaxel 80 mg/m^2 for 12 weeks (group P), followed by four cycles of FEC (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) every 21 days, and crossover was not permitted. Treatment was discontinued if progressive disease or unacceptable toxicity was noted. Dose reductions (P from 80 to 70 mg/m^2 and E from 1.4 to 1.1 mg/m^2) were permitted according to the grade of toxicity. Prophylactic granulocyte colony-stimulating factor was permitted depending on the grade of neutropenia. Patients were withdrawn from the study if they had Grade 4 non-haematological toxicity, progression while undergoing chemotherapy, or a treatment delay of 16 days due to toxicity.

Surgery was planned after completion of the stratified treatment and evaluation of the tumour. Mastectomy or breast-conserving surgery (BCS) and axillary staging was performed at the discretion of the surgeon and patient. Postoperative radiation and adjuvant therapy was administered according to the attending physician's judgement or patient preference. The stopping criteria were as follows: 1) clear clinical exacerbation of breast cancer after the start of treatment and the efficacy is determined to be progressive disease (PD); 2) protocol treatment cannot be continued due to adverse events (AEs) ((i) grade 4 non-haematological toxicity; (ii) start of the next course of chemotherapy is delayed for 3 weeks or more due to an AE; (iii) the provisions for discontinuing protocol treatment in the Treatment Change Criteria are met; (iv) an allergic reaction/hypersensitivity of grade 3 or higher develops during weekly paclitaxel); 3) the patient withdraws consent or wishes to discontinue the study; 4) the patient is found to be ineligible after the start of treatment; and 5) the investigator determines that it is difficult to continue the protocol treatment.

2.4. Assessment of safety

AEs were assessed before treatment with eribulin or paclitaxel and FEC on the day of administration. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) [17] and collected at the data centre. The worst grade of each AE for every patient was counted and reported.

In addition to CTCAE, subjective symptoms were assessed using the Japanese version of the Patient Neuropathy Questionnaire (PNQ) [18], a validated patient-reported questionnaire on neuropathy. The scoring definitions of PNQ are detailed in Table 1; patients subjectively responded to each item, and the mean scores of PNQ were calculated by averaging the collected data. PNQ was collected not only from baseline, during the intended chemotherapy, and after the administration of FEC, but also at 6 months and at 1, 2, 3, and 4 years after surgery.

Table 1
Patient Neurotoxicity Questionnaire (PNQ) score test

Score	Item 1 (sensory)	Item 2 (motor)
1	I have no numbness, pain, or tingling in my hands or feet.	I have no weakness in my arms or legs.
2	I have mild tingling, pain or numbness in my hands or feet. This does not interfere with my activities.	I have mild weakness in my arms or legs. This does not interfere with my activities.
3	I have moderate tingling, pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate weakness in my arms or legs. This does not interfere of my activities of daily living.
4	I have moderate to severe tingling, pain or numbness in my hands or feet. This interferes with my activities of daily living.	I have moderate to severe weakness in my arms or legs. This interferes with my activities of daily living.
5	I have severe tingling, pain or numbness in my hands or feet. It completely prevents me from doing most activities.	I have severe weakness in my arms or legs. It completely prevents me from doing most activities.

2.5. Assessment of efficacy

Clinical response was radiologically assessed prior to surgery as complete response (CR), partial response (PR), stable disease (SD), and PD in accordance with the Response Evaluation Criteria in Solid Tumours version 1.1 [19].

Pathological response was assessed post-surgery using haematoxylin–eosin-stained tissue samples prepared from tissue sections of primary tumours at each participating institution. Pathological complete response (pCR) was defined as no invasive residual tumour tissue in the breast. Non-invasive breast residual and infiltrated lymph nodes were permitted, as used by the National Surgical Adjuvant Breast and Bowel Project (ypT0/is ypN0/+) [20].

2.6. Endpoints

The primary endpoint was the incidence of grade 1 or higher peripheral sensory neuropathy (PSN) and peripheral motor neuropathy (PMN) according to CTCAE. This was evaluated every 3 weeks for a total of eight times during the treatment prior to surgery. Secondary endpoints were pCR, clinical response (CR+PR), BCS, AEs, PNQ, and disease-free survival (DFS).

2.7. Statistical analysis

The planned sample size was 230 cases based on the assumptions that the proportion of grade 1 or higher neuropathy in group P would be 30% and that of group E would reduce the proportion to 50%. Thus, we estimated that 105 patients would be required to detect this difference with a power of 80% and a two-sided α of 0.05. According to an estimated dropout rate of approximately 10%, the target enrolment was set at 230 patients (115 per group).

Patients who received the protocol treatment (four cycles of eribulin (E) or weekly paclitaxel 12 times (P), followed by four cycles) were included in the efficacy analysis. Those who received at least one dose of either regimen were included in the safety analysis.

For the primary endpoint, PSN and PMN rates were compared between the groups using Fisher's exact test. The secondary endpoints of clinical response rates and BCS rates were compared between the groups using the Fisher's exact test. PSN, PMN, and PNQ were also compared using Fisher's exact test. DFS was estimated using the Kaplan–Meier method and was compared between the groups using the log-rank test when the sample size was considered sufficient.

All analyses were performed using IBM SPSS Statistics Version 26 (IBM Corp., Armonk, NY, USA). A P-value of <0.05 was considered significant.

3. Results

3.1. Patient characteristics

One hundred and twenty-one participants were recruited from 10 participating institutions and registered between December 2013 and April 2016. Patients were randomised to group E (n=60) and group P (n=61) (Table 2). Three patients in group P were excluded before the protocol treatment. Two patients withdrew consent, and one could not start the protocol by the scheduled date because they were undergoing treatment for subclavian vein thrombus associated with central venous access port placement. Thus, safety was analysed in 60 patients from group E and 58 from group P. Efficacy could not be evaluated in three patients. One patient in group E discontinued treatment because of a grade 3 allergic reaction to the initial treatment, one in group E refused surgery, and one in group P dropped out of the study because she required treatment for deterioration of diabetes during chemotherapy and could not undergo the protocol treatment. Overall, 115 patients (58 from group E and 57 from group P) completed the treatment and were evaluated for efficacy (Fig. 1).

Table 2
Baseline characteristics

		Group E	Group P
		(n=60)	(n=58)
Age (years)	Median	53.5	53
	Minimum, maximum	28, 69	27, 67
ECOG PS	0	59 (98.3%)	58 (100%)
	1	0 (0%)	0 (0.0%)
	NA	1 (1.7%)	0 (0.0%)
Menopausal status	Pre	29 (48.3%)	27 (46.6%)
	Post	31 (51.7%)	31 (53.4%)
Clinical T stage	T1	7 (11.6%)	7 (12.0%)
	T2	45(75.0%)	38 (65.5%)
	T3	2 (3.3%)	5 (8.6%)
	T4	6 (10.0%)	8 (13.7%)
Nodal status (clinical)	Negative	22 (36.7%)	28 (48.3%)
	Positive	35 (58.3%)	29 (50.0%)
	NA	3 (5.0%)	1 (1.7%)
Histological type	Ductal	56 (93.3%)	53 (91.3%)
	Lobular	1 (1.7%)	1 (1.7%)
	Other	1 (1.7%)	0 (0.0%)
	NA	2 (3.3%)	4 (6.9%)
Histological grade	1	4 (6.7%)	4 (6.9%)
	2	46 (76.7%)	38 (65.5%)
	3	10 (16.7%)	16 (27.6%)
Oestrogen receptor	Positive	37 (61.7%)	38 (65.5%)
	Negative	23 (38.3%)	20 (34.5%)
HER2 status	Positive	20 (33.3%)	20 (34.5%)

ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not available.

	Group E	Group P
Negative	40 (66.7%)	38 (65.5%)
ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not available.		

3.2. Neuropathy

Incidences of PSN and PMN according to CTCAE ver.4.0. are shown in Table 5 and 6, respectively. PSN was consistently lower in group E than in group P after week 6, while PMN in group E was significantly lower at weeks 9, 12, and 15 (Fig. 2).

PNQ item 1 (sensory) and item 2 (motor) grades for the scheduled times are shown in Figures 3 and 4, respectively. PNQ item 1 (sensory) was consistently lower in group E after week 7, while item 2 (motor) in group E was consistently lower, although not significant (Fig. 3 and 4). These findings indicate that the incidence and severity of peripheral neuropathy was significantly lower in patients who received eribulin compared with those who received paclitaxel.

3.3. Pathological complete response

pCR rates were 20.7% in group E and 29.8% in group P (P=0.289; Table 3). There were no cases of pCR in the breast but with residual cancer in the lymph nodes. The overall clinical response rate was 55.2% in group E (CR, 6.9%; PR, 48.3%) and 77.2% in group P (CR, 8.8%; PR, 68.4%; P=0.017; Table 3). The rates of BCS were 56.9% in group E and 52.6% in group P (P=0.710; Table 3). Thus, paclitaxel demonstrated better pCR and clinical response rates than eribulin, but BCS rates were better in patients who received eribulin.

Table 3
Clinicopathological effects and type of surgery

	Group E (*n*=58)	Group P (*n*=57)	P-value
Clinical effect	n **(%)**	n **(%)**	
CR	4 (6.9%)	5 (8.8%)	
PR	28 (48.3%)	39 (68.4%)	
RR (CR+PR)	32 (55.2%)	44 (77.2%)	**0.017**
SD	20 (34.5%)	8 (14.0%)	
PD	4 (6.9%)	4 (7.0%)	
NE	2 (3.4%)	1 (1.8%)	
Pathological effect			
pCR	12 (20.7%)	17 (29.8%)	0.289
OR (95% CI)	0.61 (0.26–144)	1.0	
Type of surgery			
BCS	33 (56.9%)	30 (52.6%)	0.710
Mastectomy	25 (43.1%)	27 (47.4%)	

Significant associations are marked in bold. BCS, breast-conserving surgery; CI, confidence interval; CR, complete response; NE, not evaluable; OR, overall response; pCR, pathological complete response; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.

3.4. Safety

AEs are summarised in Table 4. Four (6.7%) patients in group E had febrile neutropenia, which was not experienced by patients in group P, although this was not significantly different. Moreover, neutropenia and leukocytopenia over grade 3 were significantly more frequent in group E. However, rash, nail disorder, and allergic reaction were significantly more frequent in group P.

Table 4
Adverse events

	Group E (*n*=60)		Group P (*n*=58)			
Adverse event	**Total**	**Grade 3 or 4**	**Total**	**Grade 3 or 4**	**P-value**	**P-value (Grade 3 or 4)**
	n **(%)**	n **(%)**	n **(%)**	n **(%)**	**(Total)**	
All adverse events	60 (100%)	16 (26.7%)	58 (100%)	2 (3.4%)	1.000	**<0.001**
Peripheral sensory neuropathy	40 (66.7%)	0 (0.0%)	54 (93.1%)	3 (5.2%)	**<0.001**	0.116
Peripheral motor neuropathy	16 (26.7%)	0 (0.0%)	28 (48.3%)	0 (0.0%)	**0.022**	1.000
Leukopenia	14 (23.3%)	6 (10.0%)	9 (15.5%)	0 (0.0%)	0.355	**0.028**
Neutropenia	20 (33.3%)	15 (25.0%)	14 (24.1%)	1 (1.7%)	0.313	**<0.001**
Febrile neutropenia	4 (6.7%)	4 (6.7%)	0 (0.0%)	0 (0.0%)	0.119	0.119
Alopecia	55 (91.7%)	0 (0.0%)	56 (96.6%)	0 (0.0%)	0.439	1.000
Nausea	18 (30.0%)	0 (0.0%)	15 (25.9%)	0 (0.0%)	0.684	1.000
Vomiting	2 (3.3%)	0 (0.0%)	5 (8.6%)	0 (0.0%)	0.268	1.000
Constipation	18 (30.0%)	1 (1.7%)	20 (34.5%)	0 (0.0%)	0.695	1.000
Diarrhoea	7 (11.7%)	0 (0.0%)	10 (17.2%)	0 (0.0%)	0.440	1.000
Increased ALT	4 (6.7%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0.365	1.000
Increased AST	4 (6.7%)	0 (0.0%)	2 (3.5%)	0 (0.0%)	0.680	1.000
Stomatitis	11 (18.3%)	0 (0.0%)	13 (22.4%)	0 (0.0%)	0.651	1.000
Dysgeusia	9 (15.0%)	0 (0.0%)	8 (13.8%)	0 (0.0%)	1.000	1.000
Decreased appetite	16 (26.7%)	0 (0.0%)	13 (22.4%)	0 (0.0%)	0.671	1.000

Significant associations are marked in bold. ALT, alanine aminotransferase; AST, aspartate transaminase.

	Group E (*n*=60)		Group P (*n*=58)			
Fatigue	30 (50.0%)	0 (0.0%)	33 (56.9%)	0 (0.0%)	0.467	1.000
Hand-foot syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000	1.000
Nail disorder	3 (5.0%)	0 (0.0%)	11 (19.0%)	0 (0.0%)	**0.023**	1.000
Rash	6 (10.0%)	0 (0.0%)	21 (36.2%)	0 (0.0%)	**<0.001**	1.000
Pigmentation	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	0.492	1.000
Pyrexia	8 (13.3%)	0 (0.0%)	4 (6.9%)	0 (0.0%)	0.363	1.000
Arthralgia	6 (10.0%)	0 (0.0%)	10 (17.2%)	0 (0.0%)	0.291	1.000
Headache	7 (11.7%)	0 (0.0%)	11 (19.0%)	0 (0.0%)	0.313	1.000
Oedema	4 (6.7%)	0 (0.0%)	7 (12.1%)	0 (0.0%)	0.358	1.000
Allergic reaction	2 (3.3%)	1 (1.7%)	9 (15.5%)	0 (0.0%)	**0.028**	1.000
Hepatic failure	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	0.492	0.492

Significant associations are marked in bold. ALT, alanine aminotransferase; AST, aspartate transaminase.

The median relative dose intensity (RDI) for eribulin in group E was 98.9% (25.0–102.8%) and for paclitaxel in group P was 99.2% (12.5–100.2%); the RDI for epirubicin was 94.5% (0–100.0%) in group E and 95.4% (0–130.6%) in group P. The number of patients with an RDI of 85% or more was 49 (81.7%) for eribulin and 48 (80.0%) for epirubicin in group E, and 53 (91.4%) for paclitaxel and 48 (82.8%) for epirubicin in group P. Thus, while RDI was similar between the two groups, the incidence of grade 3 or higher neutropenia and leukocytopenia was significantly higher in patients who received eribulin.

Table 5
Incidence of peripheral sensory neuropathy

	Group E (n=60)		Group P (*n*=58)		P-value*
Cycle	**n (%)**	**G1** **G2** **G3**	**n (%)**	**G1** **G2** **G3**	
After 1st cycle of eribulin or 3rd cycle paclitaxel	18 (30.0%)	17 (28.3%) 1 (1.7%) 0 (0.0%)	21 (36.2%)	19 (32.8%) 2 (3.4%) 0 (0.0%)	0.558
After 2nd cycle of eribulin or 6th cycle paclitaxel	21 (35.0%)	20 (33.3%) 1 (1.7%) 0 (0.0%)	38 (65.5%)	31 (53.4%) 7 (12.1%) 0 (0.0%)	**0.002**
After 3rd cycle of eribulin or 9th cycle paclitaxel	25 (41.7%)	24 (40.0%) 1 (1.7%) 0 (0.0%)	49 (84.5%)	30 (51.7%) 17 (29.3%) 2 (3.4%)	**<0.001**
After 4th cycle of eribulin or 12th cycle paclitaxel	31 (51.7%)	26 (43.3%) 5 (8.3%) 0 (0.0%)	52 (89.7%)	23 (39.7%) 29 (50.0%) 0 (0.0%)	**<0.001**
After FEC 1	25 (41.7%)	22 (36.7%) 3 (5.0%) 0 (0.0%)	50 (86.2%)	24 (41.4%) 26 (44.8%) 0 (0.0%)	**<0.001**
After FEC 2	23 (38.3%)	21 (35.0%) 2 (3.3%) 0 (0.0%)	47 (81.0%)	22 (37.9%) 25 (43.1%) 0 (0.0%)	**<0.001**
After FEC 3	24 (40.0%)	23 (38.3%) 1 (1.7%) 0 (0.0%)	46 (79.3%)	24 (41.4%) 21 (36.2%) 1 (1.7%)	**<0.001**

Significant associations are marked in bold. FEC, fluorouracil, epirubicin, and cyclophosphamide; G1, grade 1; G2, grade 2; G3, grade 3.

	Group E (n=60)		Group P (*n*=58)		P-value*
Cycle	**n (%)**	**G1** **G2** **G3**	**n (%)**	**G1** **G2** **G3**	
After FEC 4	21 (35.0%)	20 (33.3%) 1 (1.7%) 0 (0.0%)	46 (79.3%)	27 (46.6%) 18 (31.0%) 1 (1.7%)	**<0.001**

Significant associations are marked in bold. FEC, fluorouracil, epirubicin, and cyclophosphamide; G1, grade 1; G2, grade 2; G3, grade 3.

Table 6
Incidence of peripheral motor neuropathy

	Group E (n=60)		Group P (*n*=58)		P-value*
Cycle	**n (%)**	**G1** **G2**	**n (%)**	**G1** **G2**	
After 1st cycle of eribulin or 3rd cycle paclitaxel	13 (21.7%)	13 (21.7%) 0 (0.0%)	11 (19.0%)	11 (19.0%) 0 (0.0%)	0.820
After 2nd cycle of eribulin or 6th cycle paclitaxel	12 (20.0%)	12 (20.0%) 0 (0.0%)	15 (25.9%)	15 (25.9%) 0 (0.0%)	0.514
After 3rd cycle of eribulin or 9th cycle paclitaxel	12 (20.0%)	12 (20.0%) 0 (0.0%)	24 (41.4%)	21 (36.2%) 3 (5.2%)	**0.016**
After 4th cycle of eribulin or 12th cycle paclitaxel	15 (25.0%)	15 (25.0%) 0 (0.0%)	26 (44.8%)	21 (36.2%) 5 (8.6%)	**0.033**
After FEC 1	13 (21.7%)	13 (21.7%) 0 (0.0%)	25 (43.1%)	21 (36.2%) 4 (6.9%)	**0.018**
After FEC 2	12 (20.0%)	12 (20.0%) 0 (0.0%)	21 (36.2%)	17 (29.3%) 4 (6.9%)	0.065
After FEC 3	12 (20.0%)	12 (20.0%) 0 (0.0%)	19 (32.8%)	15 (25.9%) 4 (6.9%)	0.144
After FEC 4	12 (20.0%)	12 (20.0%) 0 (0.0%)	19 (32.8%)	17 (29.3%) 2 (3.4%)	0.144

Significant associations are marked in bold. FEC, fluorouracil, epirubicin, and cyclophosphamide; G1, grade 1; G2, grade 2.

3.5. Disease-free survival

Median follow-up of group E and group P was 54.2 and 51.4 months, respectively, and there was no significant difference between group E and group P (P=0.561, Fig. 5). Thus, no greater survival benefits were observed between eribulin and paclitaxel.

4. Discussion

NAC is one of the preferred treatment strategies for early breast cancer because it has various advantages including improved breast conservation and enhanced assessment of tumour response. However, several side effects are associated with neoadjuvant agents such as paclitaxel. We conducted this prospectively registered multicentre study with patient-relevant outcomes to explore whether eribulin followed by an anthracycline confers fewer side effects than paclitaxel, with emphasis on grade 1 or higher peripheral neuropathy. To our knowledge, this is the first prospective randomised controlled trial comparing eribulin and paclitaxel focusing on neuropathy. A significant difference in PSN was observed between eribulin and paclitaxel. However, the trial review committee of the JONIE group halted this trial because a similar study at MD Anderson had closed early due to lower pCR rates that crossed a futility stopping boundary in the eribulin group [21]. pCR rates in the current study indicated that the efficacy of eribulin was lower than that of paclitaxel, affecting prognosis.

Neuropathy should be evaluated if taxane is administered as the control because neuropathy accompanying taxanes causes severe long-term damage to quality of life, and there is currently no effective standard therapy [22, 23]. Thus, it is important to alleviate neuropathy from adjuvant chemotherapy, which occurs in certain patients, most of whom are survivors. Neuropathy was evaluated as one of several AEs in two previous trials, but to our knowledge there have been no prospective randomised controlled trials comparing neuropathy caused by eribulin with that of paclitaxel [14, 15].

In this study, the frequency and severity of neuropathy were significantly better in group E than group P. PNQ was evaluated for 4 years, and PSN was significantly better in group E. Some patients suffered from severe neuropathy (PNQ score 4 or 5; interfering with activities of daily living) in group P, which continued for several years, consistent with previous reports [24]. It remains unclear as to why some patients have long-term severe neuropathy in perioperative chemotherapy, but a previous report indicated that neuropathy induced by paclitaxel in Japanese breast cancer patients was associated with older age and a polymorphism in the *ABCB1* transporter [25]. Therefore, paclitaxel alternatives should be considered, of which eribulin could be a candidate.

Our study showed a significant difference in the response rate on imaging but no significant difference in pCR between patients who received paclitaxel or eribulin (29.8% and 20.7%, respectively; P=0.289). This contrasts with the findings of the MD Anderson trial [21], in which pCR was 27% in the paclitaxel group and 5% in the eribulin group. These differences may be because of the low number of cases receiving eribulin in the MD Anderson trial [21]. Another study comparing eribulin with paclitaxel in combination with anthracycline was performed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) [26]. Although the prognosis was not reported, they also revealed a lower pCR rate of 17% for eribulin compared with 26% for paclitaxel (not significant). Although there was no significant difference in the pCR rate between eribulin and paclitaxel followed by anthracycline, the efficacy for early breast cancer was commonly lower in the eribulin arm in the three trials. Nonetheless, the differences between the results of these previous studies and the current study are marked. One explanation is that they were conducted in different patient populations and the differences could be attributed to pharmacoethnicity, but there is currently no reported evidence of such differences for eribulin. Furthermore, while the US Food

and Drug Administration endorses pCR as a surrogate endpoint for breast cancer to enable acceleration of drug approval, a systematic review of pCR as a surrogate endpoint for DFS and overall survival in randomised trials for neoadjuvant therapy of early breast cancer questioned its reliability and suggested that it was not robust as a primary endpoint [27]. Hence, the use of pCR to assess efficacy may be misleading, and a future study examining the effect of neoadjuvant eribulin on other equivalent endpoints should be considered. Thus, caution should be exercised when comparing pCR rates between studies.

Regarding prognosis, despite there being several more patients with nodal metastases in group E at baseline, the Kaplan–Meier curve was superior in group E in this study, although not significant. However, according to Lim et al., DFS and overall survival was better for paclitaxel, but this was also not significant [15]. Because the prognostic data was not sufficient, further investigations are necessary. Eribulin was reported to promote an antitumour immune response [28], and thus it could contribute to inconsistencies in tumour shrinkage and prognosis.

No significant differences between the two groups were reported by Abraham et al. regarding other AEs [14]. However, toxicity was greater in the eribulin arm, especially neutropenia, according to Lim et al. [15]. Haematological toxicity was also more frequent and more severe in group E than group P in this study, and several patients had febrile neutropenia, which must be treated seriously. Nonetheless, eribulin caused fewer allergic reactions, and thus may represent a treatment option for patients who cannot tolerate paclitaxel.

There are several limitations of this study. The number of enrolled patients did not reach the planned sample size, and thus the statistical interpretation of the data was limited. Furthermore, the trial was stopped early, and hence the analyses of the prespecified endpoints are underpowered. The evaluation of neuropathy is subjective and thus has the potential to introduce bias, particularly because the study was not blinded. In addition, eribulin induced more severe haematological events than paclitaxel, and therefore the choice to administer eribulin would need to be justified on a patient-by-patient basis in consideration of these effects. Nonetheless, a strength of this study is that there were notable differences in the AEs between eribulin and paclitaxel.

5. Conclusions

In conclusion, eribulin resulted in less frequent and less severe peripheral neuropathy than paclitaxel. While eribulin was not more effective than weekly paclitaxel, and it conferred more frequent and more severe haematological AEs than paclitaxel, eribulin could be an alternative to weekly paclitaxel in perioperative chemotherapy. Future studies should focus on analysing a subgroup of early-stage breast cancer patients with neuropathy to assess non-inferiority with regards to efficacy using alternative endpoints to pCR, and to confirm the neuropathy outcome. A subgroup analysis of such a study should also be conducted to determine if efficacy observations are dependent on ethnic background.

Declarations

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Competing Interests

The authors declare that they have no potential conflicts of interest.

Author Contributions

D.M. designed this phase 2 trial. K.N., T.I., K.N., D.M., Y.H., A.T., J.H., M.H., M.M., T.K, M.S., N.K., and T.I. were the site investigators who recruited patients, contributed to patient care, and collected patient data. K.A. was the bioinformatician who managed the data centre and analysed and summarised the acquired data statistically. T.I. guided the initial drafting of the manuscript, and K.N. drafted, refined, and edited the manuscript. T.I., D.M., and Y.H. reviewed the manuscript. All authors had full access to the study data, contributed to the revision and approval of the manuscript, and participated in the decision to submit the manuscript for publication.

Data Availability

The data underlying this study were collected and analysed at the Department of Medical Informatics, Niigata University Medical and Dental Hospital, Niigata, Japan. Data will be shared on request to the corresponding author with the permission of JONIE.

Ethics Approval

The study complied with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research of the Ministry of Health, Labour and Welfare of Japan. The study protocol was reviewed and approved by the institutional review board of each participating institution.

Consent to Participate

All patients provided written informed consent at primary registration.

Consent to Publish

All authors contributed to this study and provided consent for publishing.

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Figures

Fig. 1

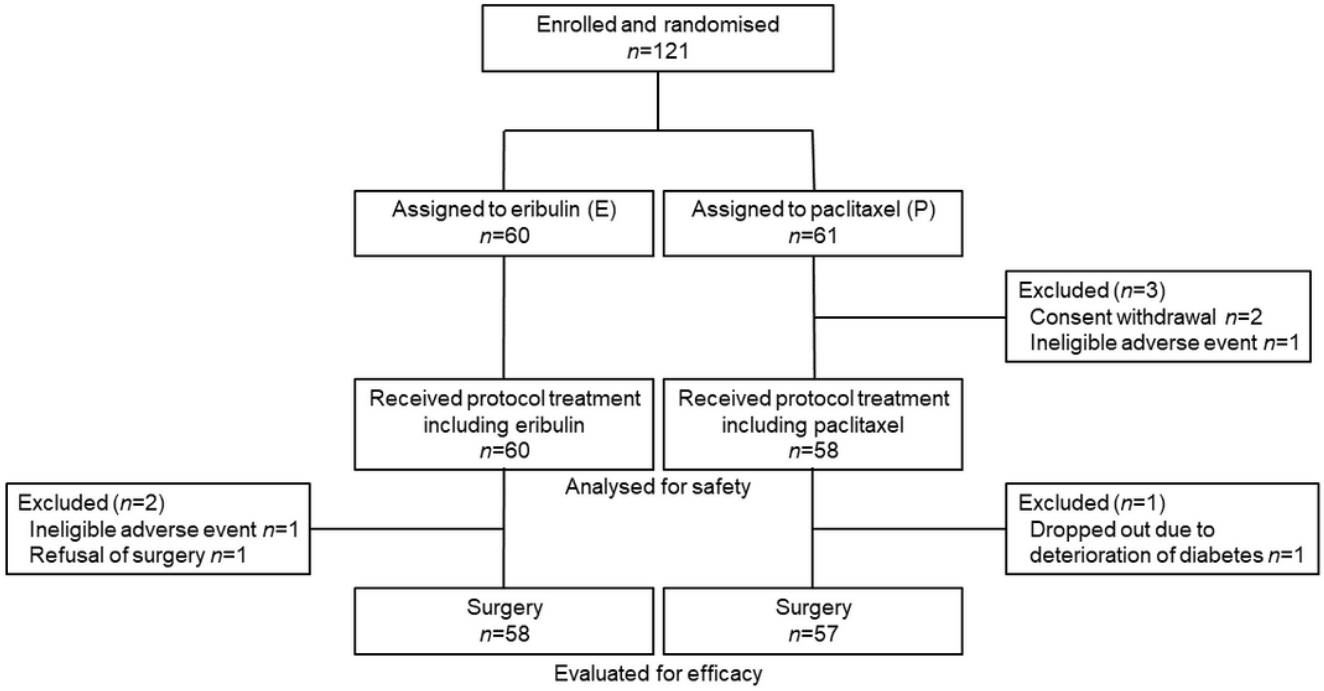


Figure 1

CONSORT diagram.

Fig. 2

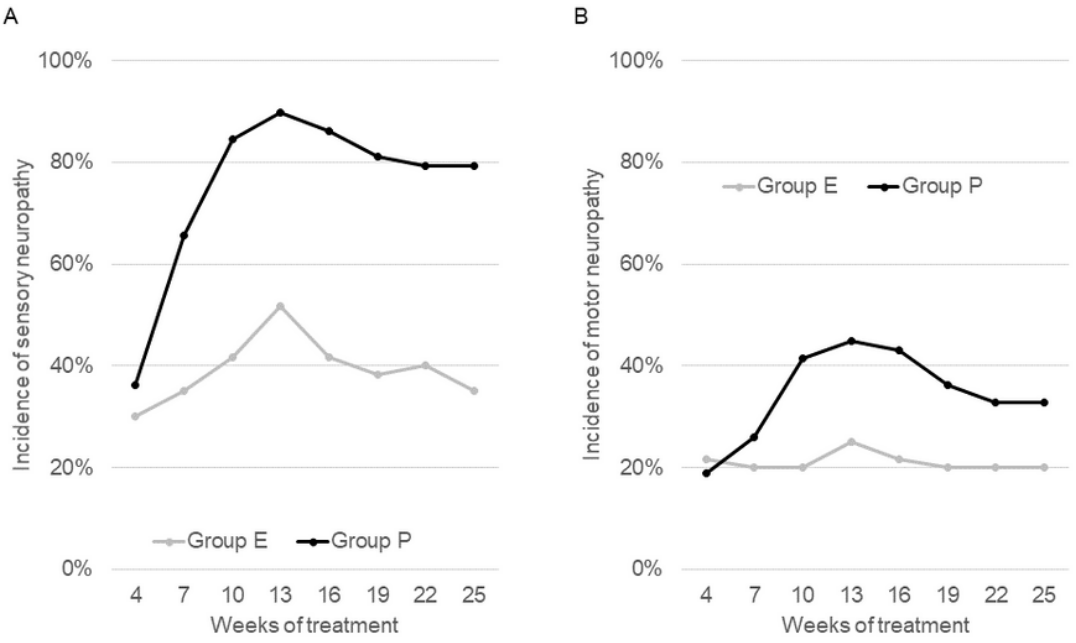


Figure 2

Incidences of grade 1 or higher peripheral sensory neuropathy (A) and peripheral motor neuropathy (B) according to CTCAE ver.4.0.

Fig. 3

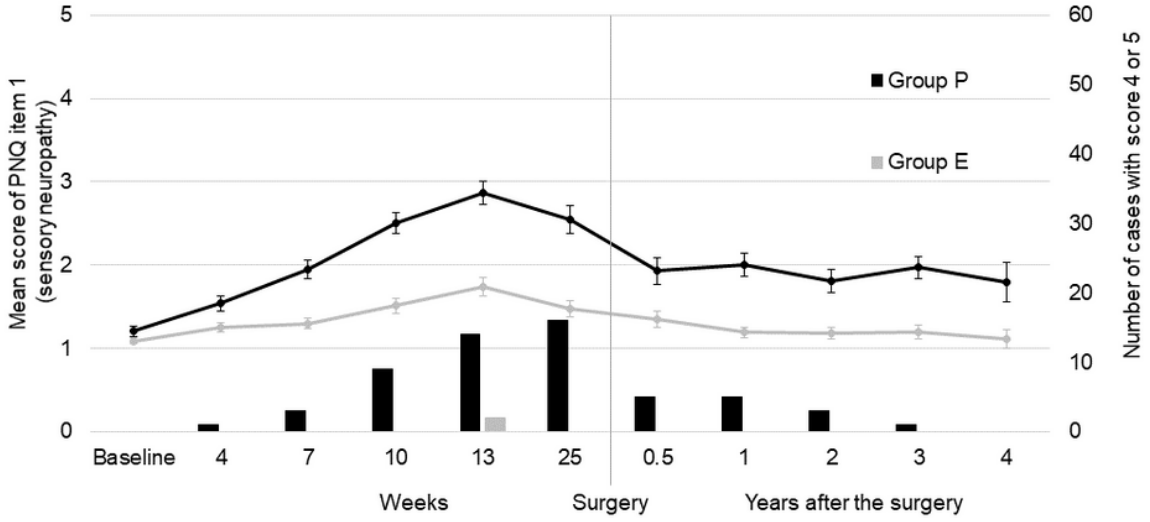


Figure 3

Mean scores (line graph) of PNQ item 1 (sensory) and number of cases with a score of 4 or 5 (bar graph). Error bars indicate standard deviation.

Fig. 4

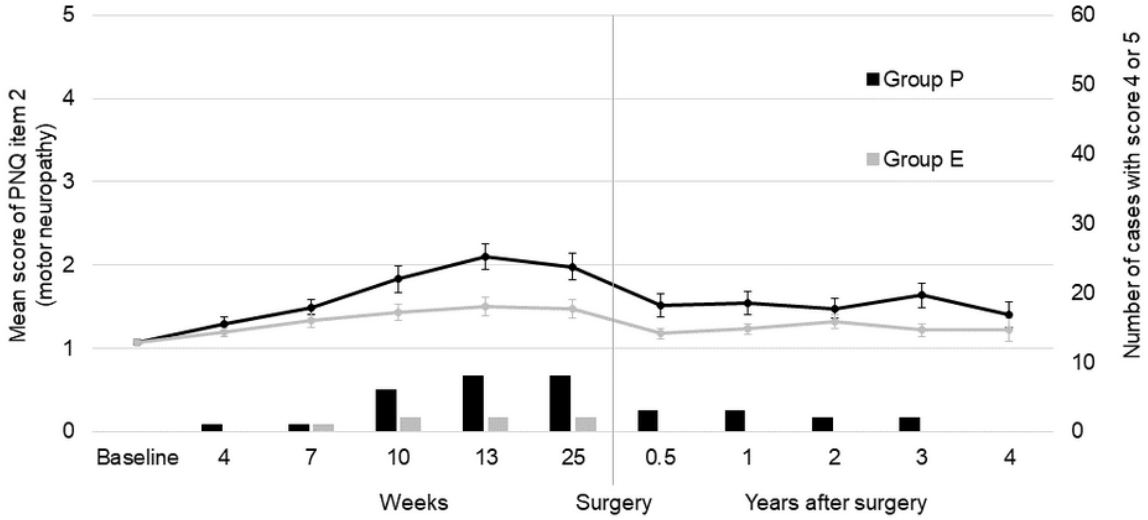
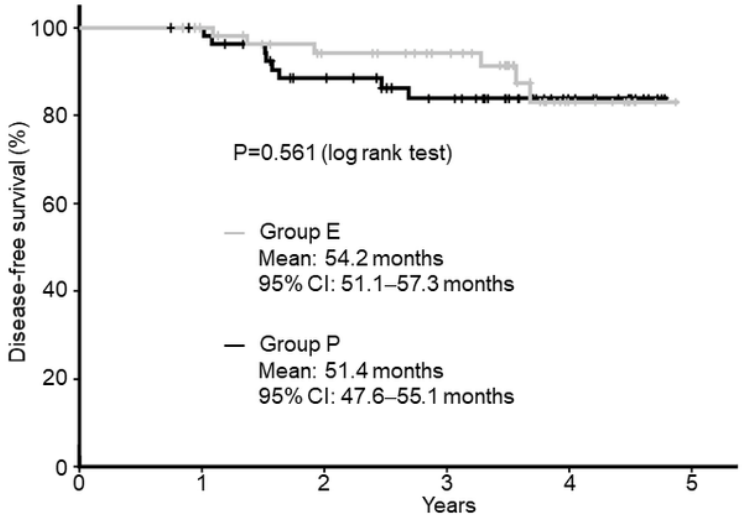


Figure 4

Mean scores (line graph) of PNQ item 2 (motor) and number of cases with a score of 4 or 5 (bar graph). Error bars indicate standard deviation.

Fig. 5



Patients at risk	Total	1 years	2 years	3 years	4 years	Events
Group P	57	54	43	34	14	8
Group E	58	54	44	38	11	6

Figure 5

Disease-free survival of each group.