Journal of the National Cancer Center 4 (2024) 135–141

Contents lists available at ScienceDirect

Journal of the National Cancer Center

journal homepage: www.elsevier.com/locate/jncc

Full Length Article

Efficacy and safety of paclitaxel liposome versus paclitaxel in combination with carboplatin in the first-line chemotherapy for ovarian cancer: a multicenter, open-label, non-inferiority, randomized controlled trial

Rong Li[1], Hongping Zhang[2], Qingshui Li[3], Guangwen Yuan[4], Yanjie Zhou[5], Rutie Yin[6], He Wang[7], Chunyan Wang[8], Yi Huang[9], Wei Wang[10], Xiaojian Yan[11], Lingying Wu[4,*], Qi Zhou[1,*]

[1] *The Gynecologic Oncology Center, Chongqing University Cancer Hospital, Chongqing, China*
[2] *Department of Gynecologic, Yunnan Cancer Hospital, Kunming, China*
[3] *Department of Gynecologic Oncology, Shandong Cancer Hospital, Jinan, China*
[4] *Department of Gynecologic Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*
[5] *Department of Gynecologic Oncology, Hunan Cancer Hospital, Changsha, China*
[6] *Department of Tumor Radiotherapy and Chemotherapy, West China Second University Hospital of Sichuan University, Chengdu, China*
[7] *Department of Gynecologic, Guangxi Cancer Institute, Nanning, China*
[8] *Department of Gynecologic Oncology, Liaoning Cancer Hospital, Shenyang, China*
[9] *Department of Gynecologic Oncology, Hubei Cancer Hospital, Wuhan, China*
[10] *The Gynecologic Oncology Center, Peking Union Medical College Hospital, Beijing, China*
[11] *Department of Gynecologic, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China*

ARTICLE INFO

Keywords:
Ovarian cancer
Paclitaxel liposome
First-line chemotherapy
Efficacy
Safety

ABSTRACT

Background: The paclitaxel liposome formulation, encapsulating paclitaxel within a phospholipid bilayer, addresses the insolubility of traditional paclitaxel formulations, thereby reducing toxicity without compromising its antitumor efficacy.

Methods: This multicenter, open-label, non-inferiority randomized controlled trial (ChiCTR2000038555) evaluates the efficacy and safety of paclitaxel liposome in comparison to the standard regimen of paclitaxel combined with carboplatin (PLC vs. PC) as first-line therapy in patients with epithelial ovarian cancer.

Results: An analysis of median progression-free survival (PFS) revealed non-inferior outcomes between 263 patients in the PLC group and 260 patients in the PC group (32.3 vs. 29.9 months, hazard ratio [HR], 0.89 [95% CI, 0.64–1.25]), using a non-inferior margin of 1.3. Although the overall incidence of treatment-related adverse events was comparable between groups, the PLC group experienced significantly fewer non-hematologic toxicities than those treated with the PC regimen.

Conclusion: The findings affirm the non-inferiority of paclitaxel liposome compared to the combination of paclitaxel and carboplatin regarding therapeutic efficacy, with an enhanced safety profile marked by reduced non-hematologic toxicities.

1. Introduction

Ovarian cancer ranks as the eighth most prevalent cancer and the eighth leading cause of cancer-related mortality among women, posing a significant threat to women's health globally.[1,2] The absence of effective screening and early diagnostic strategies results in approximately 72.0% of patients being diagnosed with advanced-stage disease.[3] In the realm of first-line chemotherapy for ovarian cancer, the combination of paclitaxel and carboplatin administered every three weeks stands as the cornerstone of treatment and the regimen of choice.[4] Although the paclitaxel-carboplatin regimen is associated with survival benefits for ovarian cancer patients, the formulation of paclitaxel poses challenges due to its poor aqueous solubility (less than 0.03 mg/ml), complicating its preparation for intravenous administration. To address this issue, paclitaxel is commonly dissolved in mixed solvents, including Cremophor EL (polyoxyethylated castor oil), for clinical use.[5] However, the

* Corresponding authors.
E-mail addresses: wulingying@csco.org.cn (L. Wu), qizhou9128@163.com (Q. Zhou).

https://doi.org/10.1016/j.jncc.2024.04.004
Received 7 December 2023; Received in revised form 18 April 2024; Accepted 23 April 2024

biological activity of Cremophor EL can lead to severe adverse effects, such as hypersensitivity reactions, nephrotoxicity, and neurotoxicity, necessitating the interruption, reduction, or discontinuation of chemotherapy in some cases.[6]

The innovation of the paclitaxel liposome formulation, which encapsulates paclitaxel within a liposomal phospholipid bilayer, offers a solution to the solubility challenge.[7] This novel drug delivery system has been shown to significantly increase the maximum tolerated dose by 2–7-fold relative to traditional solvent-based paclitaxel, while concurrently reducing toxicity without undermining antitumoral efficacy.[8,9] Furthermore, paclitaxel liposomes have demonstrated therapeutic activity across a spectrum of advanced solid tumors, including but not limited to breast cancer,[10] lung squamous cell carcinoma,[11] esophageal squamous cell carcinoma,[12] gastric cancer,[13] and nasopharyngeal carcinoma.[14]

Recently, the combination of paclitaxel liposomes and platinum-based compounds has emerged as a widely adopted chemotherapy regimen for epithelial ovarian cancer, noted for its safety and efficacy. The improved safety profile of paclitaxel liposomes in the treatment of advanced ovarian cancer has been supported by several small-scale retrospective studies conducted in China.[15-19] Despite these findings, there remains a lack of randomized controlled trials directly comparing the efficacy and safety of paclitaxel liposome with the standard regimen of paclitaxel in combination with carboplatin for first-line chemotherapy in patients with epithelial ovarian cancer. This study, therefore, aims to fill this gap by evaluating the efficacy and safety of paclitaxel liposomes versus the conventional paclitaxel-carboplatin combination as the first-line chemotherapy treatment in patients with epithelial ovarian cancer.

2. Material and methods

2.1. Study design and patients

This multicenter, open-label, non-inferiority randomized controlled trial enrolled patients diagnosed with stage II-IV primary ovarian, peritoneal, or fallopian tube cancer who had undergone R0/R1 primary or interval debulking surgery. Recruitment spanned from August 2017 to July 2021 across 11 centers in China. Eligibility criteria included: (1) age between 18 and 75 years; (2) confirmed primary ovarian, peritoneal, or fallopian tube cancer of stages II-IV, as determined by pathology and/or cytology; (3) comprehensive cytoreductive surgery entailing complete hysterectomy, bilateral adnexectomy, omentectomy, lymph node dissection, and removal of all visible disease; (4) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; (5) a life expectancy of at least 6 months; and (6) normal hematologic parameters with adequate hepatic and renal function. Exclusion criteria were: (1) non-epithelial ovarian, fallopian tube, or peritoneal carcinomas; (2) concurrent primary malignancies; (2) neurological or mental disorders impairing cognitive function, inclusive of central nervous system metastases; and (3) existing specific peripheral neuropathy or related symptoms. Comprehensive study design and eligibility criteria are detailed in the trial registry (ChiCTR2000038555) available at http://www.chictr.org.cn/index.aspx.

2.2. Procedures

Participants who met the eligibility criteria were enrolled and stratified via a central dynamic randomization method in a 1:1 ratio to receive either paclitaxel liposomes combined with carboplatin (PLC) or standard paclitaxel in conjunction with carboplatin (PC). This process did not involve blinding; thus, both patients and investigators were aware of the treatment allocations.

Treatment was administered in 21-day cycles, continuing until either disease progression, the withdrawal of consent by the patient, or the emergence of intolerable toxicity, for a maximum of 6 to 8 cycles. Specifically, the PLC group received an intravenous infusion of paclitaxel liposome at a dosage of 175 mg/m^2 (with permissible dose modifications of up to ±5% based on individual tolerance) over 3 h on the first day, followed by carboplatin, calculated to an area under the curve (AUC) of 5, on day one or two. The PC group underwent a parallel regimen, with paclitaxel at 175 mg/m^2 and carboplatin AUC of 5 administered under identical conditions. Prophylactic treatment with dexamethasone, diphenhydramine, and H2 receptor antagonists (such as cimetidine or ranitidine) was recommended prior to the administration of paclitaxel or its liposomal formulation, in accordance with the study protocol or prevailing clinical guidelines. The use of additional anti-tumor therapies was prohibited during the trial period.

Following the conclusion of the treatment, participants were monitored at three-month intervals for up to 24 months to assess disease progression. In cases where a participant exited the study due to adverse events (AEs), follow-up assessments were continued until the AE was resolved, ameliorated, or stabilized, as determined by the clinical judgment of the investigators.

2.3. Endpoints

The primary endpoint was progression-free survival (PFS), delineated as the duration from randomization to either the onset of disease progression, as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or mortality from any cause, whichever occurred first. Secondary endpoints encompassed AEs. Treatment-related adverse events (TRAEs) were documented, detailing symptoms, severity (graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events 4.03), onset, management strategies, follow-up, and eventual outcomes.

2.4. Statistical analysis

The recruitment phase spanned 16 months, with the overall study duration extending to 48 months. Participants were distributed evenly in a 1:1 allocation. Drawing on prior research, the median PFS observed with paclitaxel and carboplatin therapy was established at 17.3 months.[20] To achieve statistical robustness with a one-sided α of 0.025, a power (β) of 0.20, and a non-inferiority margin defined by a hazard ratio (HR) threshold of 1.3, 596 patients was deemed necessary, factoring in a projected dropout rate of 10%.

Efficacy assessments were conducted using the full analysis set (FAS) and the per-protocol set (PPS). The FAS comprised all individuals who had received a minimum of one dose of the investigational medications, adhering to the intention-to-treat principle. The PPS included those who completed the trial in compliance with the protocol, exhibited satisfactory adherence, avoided prohibited medications during the study period, and fulfilled all case report form requirements. Missing data were not imputed. Safety evaluations were based on the safety analysis set (SS), including all participants who had received at least one dose of the study drugs and had available post-treatment safety data.

Statistical analyses were performed utilizing SAS software version 9.4. Continuous variables following a normal distribution were presented as mean ± standard deviation, while categorical variables were summarized as counts and percentages, undergoing comparison via chi-squared or Fisher's exact tests as appropriate. The median PFS, alongside the PFS rate and their respective 95% confidence intervals (CIs), were estimated using the Kaplan-Meier method and compared across groups with the log-rank test. The Cox proportional hazards model facilitated the estimation of HR and its 95% CI. An upper 95% CI limit for HR < 1.3 was indicative of non-inferiority in the context of PFS interpretation. A two-sided $P < 0.05$ was considered indicative of statistical significance when comparing safety parameters between groups.

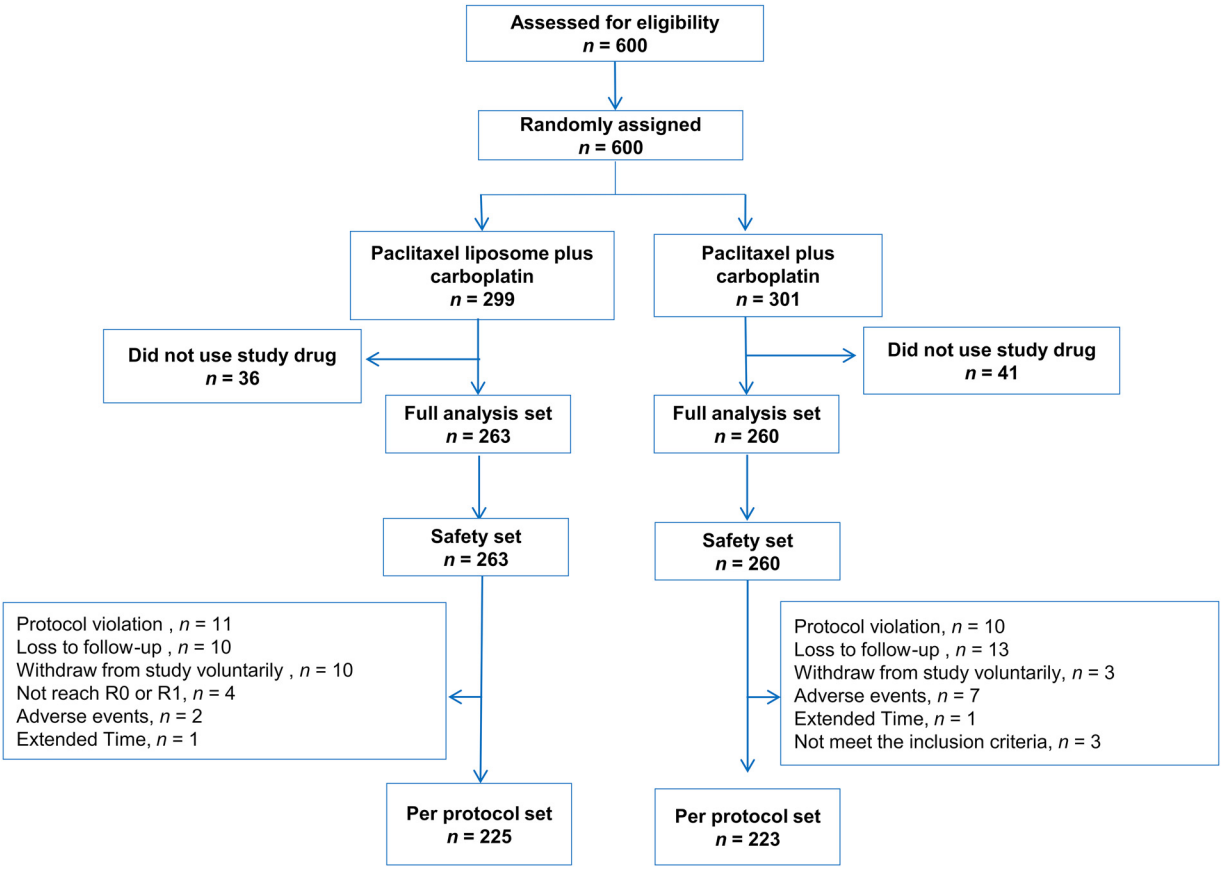

Fig. 1. Study flowchart.

3. Results

3.1. Patient characteristics

Between August 2017 and July 2021, 600 patients with stage II-IV primary ovarian, peritoneal, or fallopian tube cancer were recruited in this study spanning 11 centers across China. The study flowchart is depicted in Fig. 1. Notably, 77 participants did not proceed with the study medication administration (36 from the PLC group and 41 from the PC group), resulting in a dropout rate of 12.8%. Additionally, 75 patients were excluded from the PPS owing to deviations from the study protocol. Ultimately, the FAS and the SS comprised 263 participants in the PLC group and 260 in the PC group. Correspondingly, the PPS included 225 and 223 participants in the PLC and PC groups, respectively. Median follow-up durations were 6.1 months for the PLC group and 5.4 months for the PC group. Demographic and baseline characteristics were well-balanced between the treatment groups as detailed in Table 1.

3.2. Treatment exposure

Analysis revealed the average number of chemotherapy cycles to be 5.0 ± 2.1 for the PLC group and 5.1 ± 2.1 for the PC group. Specifically, the mean total dose received by the PLC group was 1283.8 ± 550.1 mg for paclitaxel liposome and 2842.3 ± 1367.2 mg for carboplatin. Comparatively, in the PC group, the mean total doses were 1291.6 ± 540.0 mg for paclitaxel and 2870.8 ± 1296.5 mg for carboplatin. Throughout the treatment, 79.5% of the PLC group patients and 80.4% of the PC group patients received the predefined chemotherapy regimen doses. A minority of participants received poly (adenosine diphosphate-ribose) polymerase inhibitors as part of their treatment regimen: 5 (1.90%) patients in the PLC group and 10 (3.85%) patients in the PC group.

3.3. Efficacy

In the FAS, median PFS reached 32.3 months (95% CI, 21.8–not estimated [NE]) in the PLC group, compared to 29.9 months (95% CI, 21.0–49.4) in the PC group, respectively (HR, 0.89 [95% CI, 0.63–1.25]) (Fig. 2). This demonstrates the non-inferiority of the PLC regimen to the PC regimen regarding PFS, with the upper confidence limit remaining below the pre-specified non-inferiority HR margin of 1.3. PFS rates at 6 months, 12 months, and 18 months were 95.8%, 83.3%, and 65.0% for the PLC group, and 94.4%, 79.2%, and 63.9% for the PC group, respectively (Table 2). PFS analysis within the PPS echoed these findings: 32.3 months (95% CI, 21.8–NE) versus 27.6 months (95% CI, 21.0–49.4), with an HR of 0.89 (95% CI, 0.64–1.25).

3.4. Safety

Regarding safety, 218 participants (82.9%) in the PLC group and 231 participants (88.9%) in the PC group experienced TRAEs. Among these, 91 (34.6%) patients in the PLC group and 89 (34.2%) in the PC group encountered grade 3 or higher TRAEs. The incidence of AEs, including those of grade 3 or higher, AEs necessitating dose reductions, dose interruptions, and treatment discontinuations, did not significantly differ between the groups ($P > 0.05$) (Table 3).

The predominant TRAEs in the PLC group were anemia (62.7%), white blood cell count decreased (54.4%), followed by neutrophil count decreased (50.6%), lymphocyte count decreased (38.8%), and platelet

Table 1
Baseline characteristics of patients in the full analysis set.

Variables	PLC (n = 263)	PC (n = 260)	Total (n = 523)
Age, mean±SD, years	54.1 ± 9.4	54.3 ± 8.3	54.2 ± 8.9
BMI, mean±SD, kg/m^2	22.8 ± 2.9	23.1 ± 3.4	23.0 ± 3.2
ECOG PS score, No. (%)			
0	47 (17.9)	48 (18.5)	95 (18.2)
1	162 (61.6)	165 (63.5)	327 (62.5)
2	26 (9.9)	24 (9.2)	50 (9.6)
Unknown	28 (10.7)	23 (8.9)	51 (9.8)
Pathological type, No. (%)			
Serous adenocarcinoma	194 (73.8)	188 (72.3)	382 (73.0)
Mucinous adenocarcinoma	4 (1.5)	1 (0.4)	5 (1.0)
Clear cell adenocarcinoma	11 (4.2)	8 (3.1)	19 (3.6)
Endometrioid adenocarcinoma	5 (1.9)	11 (4.2)	16 (3.1)
Others	8 (3.0)	8 (3.1)	16 (3.1)
Unknown	41 (15.6)	44 (16.9)	85 (16.3)
Differentiation degree, No. (%)			
High-grade	190 (72.2)	182 (70.0)	372 (71.1)
Low-grade	24 (9.1)	24 (9.2)	48 (9.2)
Unknown	49 (18.6)	54 (20.8)	103 (19.7)
Disease stage, No. (%)			
II	42 (16.0)	43 (16.5)	85 (16.3)
III	149 (56.7)	146 (56.2)	295 (56.4)
IV	30 (11.4)	27 (10.4)	57 (10.9)
Unknown	42 (16.0)	44 (16.9)	86 (16.4)
Neoadjuvant chemotherapy, No. (%)	68 (30.6)	55 (25.5)	123 (28.1)
Type of surgical excision, No. (%)			
PDS	153(58.2)	168 (64.6)	321 (61.4)
IDS	94 (35.7)	77 (29.6)	171 (32.7)
Unknown	16 (6.1)	15 (5.8)	31(5.9)
Degree of surgical excision in PDS, No. (%)*			
R0	117 (76.5)	132 (78.6)	249 (77.6)
R1	27 (17.7)	23 (13.7)	50 (15.6)
Unknown	9 (5.9)	13 (7.7)	22 (6.9)
Degree of surgical excision in IDS, No. (%)*			
R0	49 (52.1)	43 (55.8)	92 (53.8)
R1	19 (20.2)	11 (14.3)	30 (17.5)
Unknown	26 (27.7)	23 (29.9)	49 (28.7)

* The proportion was calculated based on the number of patients who received PDS (n = 321 in total, 153 in PLC group and 168 in PC group) or IDS (n = 171 in total, 94 in PLC group and 77 in PC group), respectively.
Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; IDS, interval debulking surgery; PC, paclitaxel plus carboplatin; PDS, primary debulking surgery; PLC, paclitaxel liposome plus carboplatin; R, resection margin; SD, standard deviation.

Table 2
Progression-free survival in two groups in the full analysis set.

Variables	PLC (n = 263)	PC (n = 260)	HR (95% CI)	P
Full analysis set				
Median PFS (95% CI), months	32.3 (21.8–NE)	29.9 (21.0–49.4)	0.89 (0.63–1.25)	
6-months rate (95% CI), %	95.8 (91.8–97.9)	94.4 (89.5–97.1)		0.5491
12-months rate (95% CI), %	83.3 (76.0–88.6)	79.2 (71.1–85.2)		0.3795
18-months rate (95% CI), %	65.0 (56.0–72.7)	63.9 (54.7–71.6)		0.8473
Per protocol set				
Median PFS (95% CI), months	32.3 (21.8–NE)	27.6 (21.0–49.4)	0.89 (0.64–1.25)	
6-months rate (95% CI), %	95.7 (91.6–97.9)	94.4 (89.5–97.1)		0.5750
12-months rate (95% CI), %	83.2 (75.8–88.5)	79.1 (71.1–85.2)		0.3952
18-months rate (95% CI), %	64.9 (55.9–72.7)	63.9 (54.7–71.6)		0.8600

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimated; PC, paclitaxel plus carboplatin; PFS, progression-free survival; PLC, paclitaxel liposome plus carboplatin.

count decreased (38.0%). In contrast, the most frequent TRAEs within the PC group included anemia (65.4%), neutrophil count decreased (53.1%), white blood cell count decreased (50.8%), nausea (44.2%), and lymphocyte count decreased (39.6%) (Table 4). Notably, the PLC group exhibited significantly lower incidences of certain non-hematologic toxicities compared to the PC group, including nausea (32.7% vs. 44.2%, P = 0.007), vomiting (21.3% vs. 34.2%, P = 0.001), decreased appetite (5.7% vs. 13.9%, P = 0.002), hyponatremia (5.3% vs. 11.2%, P = 0.017), alopecia (5.7% vs. 11.5%, P = 0.019), neurotoxicity (4.2% vs. 16.5%, P < 0.000), and hypertriglyceridemia (1.9% vs. 5.8%, P = 0.023) (Table 4).

4. Discussion

In this prospective, multicenter, non-inferiority randomized controlled trial, we assessed the efficacy and safety of paclitaxel liposome

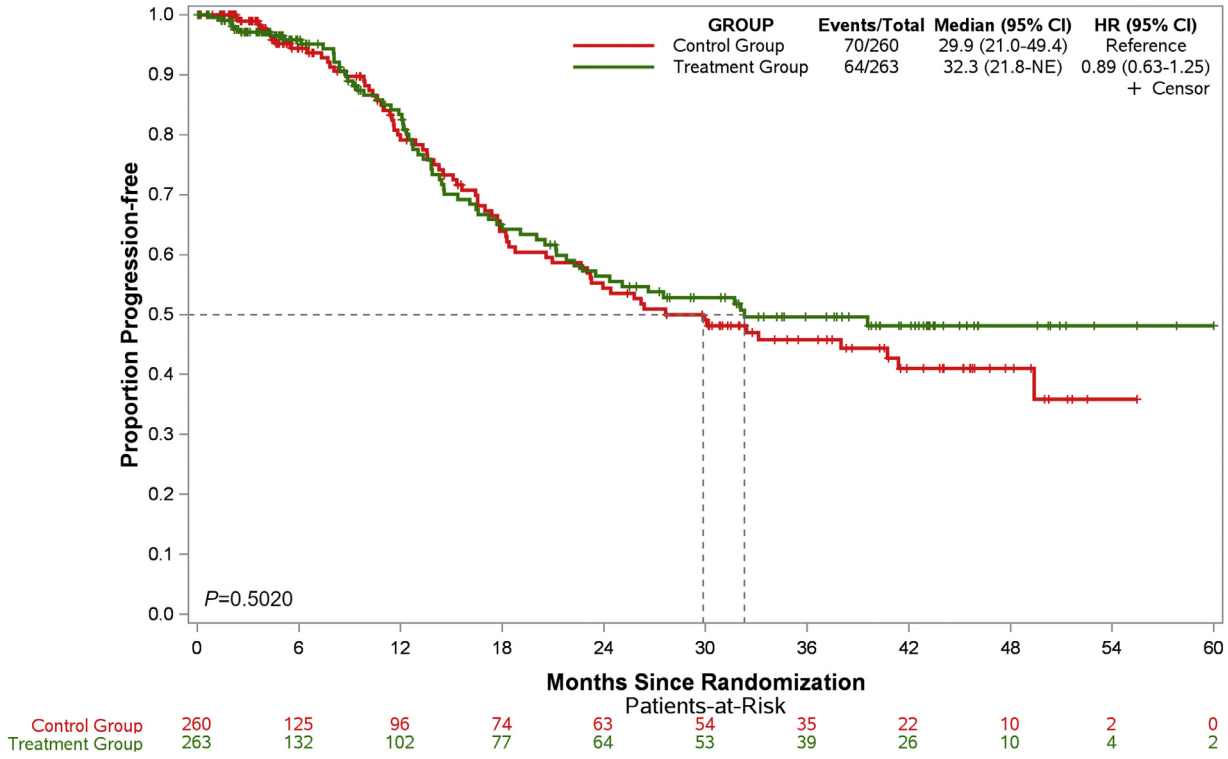

Fig. 2. Kaplan-Meier curve of progression-free survival in full analysis sets. CI, confidence interval; HR, hazard ratio. Control group, paclitaxel in conjunction with carboplatin; Treatment group, paclitaxel liposomes combined with carboplatin.

Table 3
Treatment-emergent adverse events and treatment-related adverse events in two groups in the safety analysis set.

Events	PLC group (n = 263) No. (%)	PC group (n = 260) No. (%)	P
TEAE	236 (89.7)	240 (91.5)	0.3595
TRAE	218 (82.9)	231(88.9)	0.0597
TEAE leading to dose reduction	23 (8.8)	25 (9.6)	0.7636
TRAE leading to dose reduction	22 (8.4)	24 (9.2)	0.7593
TEAE leading to dose interruption	5 (1.9)	4 (1.5)	1.0000
TRAE leading to dose interruption	5 (1.9)	4 (1.5)	1.0000
TEAE leading to treatment discontinuation	2 (0.8)	2 (0.8)	1.0000
TRAE leading to treatment discontinuation	2 (0.8)	2 (0.8)	1.0000
Grade 3 or higher TEAE	112 (42.6)	110 (42.3)	1.0000
Grade 3 or higher TRAE	91 (34.6)	89 (34.2)	1.0000

Abbreviations: PC, paclitaxel plus carboplatin; PLC, paclitaxel liposome plus carboplatin; TEAE, treatment-emergent adverse events; TRAE, treatment-related adverse events.

Table 4
Treatment-related adverse events occurring in at least 20% of patients or with significant difference.

Events	PLC (n = 263) No. (%)	PC (n = 260) No. (%)	P
Anemia	165 (62.7)	170 (65.4)	0.5846
White blood cell count decreased	143 (54.4)	132 (50.8)	0.4312
Neutrophil count decreased	133 (50.6)	138 (53.1)	0.5998
Lymphocyte count decreased	102 (38.8)	103 (39.6)	0.8582
Platelet count decreased	100 (38.0)	92 (35.4)	0.5863
Nausea	86 (32.7)	115 (44.2)	0.0071
Albumin decreased	69 (26.2)	73 (28.1)	0.6942
Alanine aminotransferase increased	66 (25.1)	71 (27.3)	0.6192
Eosinophil count decreased	62 (23.6)	48 (18.5)	0.1638
Aspartate aminotransferase increased	61 (23.2)	58 (22.3)	0.8352
Vomiting	56 (21.3)	89 (34.2)	0.0012
Decreased appetite	15 (5.7)	36 (13.9)	0.0018
Alopecia	15 (5.7)	30 (11.5)	0.0193
Hyponatremia	14 (5.3)	29 (11.2)	0.0169
Neurotoxicity	11 (4.2)	43 (16.5)	< 0.0001
Hypertriglyceridemia	5 (1.9)	5 (5.8)	0.0232

Abbreviations: PC, paclitaxel plus carboplatin; PLC, paclitaxel liposome plus carboplatin.

in combination with carboplatin versus traditional paclitaxel with carboplatin as the first-line treatment for patients with stage II-IV primary ovarian, peritoneal, or fallopian tube cancer. To our knowledge, this represents the first study directly comparing the utility of paclitaxel liposome with paclitaxel in conjunction with carboplatin for managing epithelial ovarian cancer. The findings indicate that paclitaxel liposome is non-inferior to paclitaxel in efficacy and offers superior safety profiles, particularly regarding certain non-hematologic toxicities. Thus, the combination of paclitaxel liposome and carboplatin emerges as a viable and safe alternative for first-line treatment.

Traditionally, a regimen of paclitaxel and carboplatin, administered tri-weekly, has been the established first-line chemotherapy for ovarian cancer.[4] A phase III clinical trial comparing paclitaxel plus cisplatin with paclitaxel plus carboplatin for the first-line treatment of stage III advanced ovarian cancer revealed median PFS of 20.7 months in the paclitaxel plus carboplatin group versus 19.4 months in the paclitaxel plus cisplatin group.[21] Reflecting on these outcomes, our study's paclitaxel liposomes demonstrated comparable efficacy to conventional paclitaxel, yielding median PFS of 32.3 months and 29.9 months, respectively. Furthermore, there was no significant variance in PFS rates at 6, 12, and 18 months between the two groups. Aligning with previous studies,[21-23] our results advocate for the feasibility of utilizing paclitaxel liposome in combination with carboplatin as a first-line intervention for epithelial ovarian cancer.

In this study, we observed a significantly lower incidence of certain non-hematologic TRAEs, including nausea, vomiting, reduced appetite, alopecia, and neurotoxicity, in the PLC group compared to the PC group. Solvent-based paclitaxel has been implicated in various toxicities, such as nausea, vomiting, neurotoxicity, and myalgia.[24] Notably, paclitaxel liposomes, in a Chinese study, demonstrated reduced gastrointestinal and neurological toxicity.[19] Furthermore, a comparative analysis conducted at Ningbo First Hospital, China, assessed paclitaxel liposome against paclitaxel plus carboplatin as first-line therapy for advanced ovarian cancer.[25] The findings revealed no significant differences in response rates between the groups, yet the prevalence of muscle and joint pain, dyspnea, nausea, vomiting, facial flushing, peripheral neurotoxicity, and rash was notably lower among participants receiving paclitaxel liposome. These outcomes align with those presented in our study.

Peripheral neuropathy represents a notable concern with paclitaxel use, posing a significant challenge for both clinicians and patients. Paclitaxel-induced peripheral neuropathy may persist or even worsen post-therapy cessation. Preclinical studies indicate that polyoxyethylene-substituted castor oil, used as a solvent, can lead to axonal swelling, degeneration, and demyelination, potentially contributing to the sustained neuropathy observed with paclitaxel administration.[26] The alternative solvent in paclitaxel liposomes may confer a more favorable neurotoxicity profile. This study corroborated such an advantage, with a markedly lower incidence of peripheral neurotoxicity in the PLC group than in the PC group, a finding supported by a meta-analysis.[27]

This study's limitations include the exclusive availability of paclitaxel liposomes in China, restricting our analysis to the Chinese population. Consequently, the efficacy and safety of paclitaxel liposomes plus carboplatin in diverse ethnic groups remain to be elucidated. Besides, our study's robustness is partially limited by a subset of participants for whom the pathological type and disease stage were categorized as "unknown" due to factors such as insufficient biopsy samples, incomplete pathology reports, or the loss of medical records during patient transfer between institutions. Additionally, while this study provides valuable insights into PFS, we acknowledge that OS was not assessed, and the follow-up period was limited to 24 months. The absence of OS data and a longer follow-up may restrict the comprehensiveness of long-term efficacy and safety outcomes, which are essential for the complete evaluation of first-line chemotherapy regimens in ovarian cancer.

5. Conclusions

This multicenter, non-inferiority, randomized controlled trial offered the first evidence that paclitaxel liposome in combination with carboplatin demonstrates non-inferior efficacy compared to paclitaxel plus carboplatin as a first-line treatment for ovarian cancer. Notably, it also showed enhanced safety, particularly in reducing nausea, vomiting, decreased appetite, alopecia, and neurotoxicity. These findings advocate for the PLC regimen as an effective and safe first-line therapeutic alternative.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

This trial was conducted in accordance with the Declaration of Helsinki. All protocol and amendments were approved by the independent ethics committee or institutional review board of each participating study center. All the patients provided written informed consent before any procedure.

Acknowledgement

In this study, the authors would like to thank the investigators, patients, and their families. We would also like to thank the Nanjing Luye Pharmaceutical Co., LTD., China for the provision of study drug. This research was funded by the Optimization Study of Treatment Regimen and Clinical Practice in Ovarian Cancer (grant number: 2016YFC1303702).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Q.Z. and L.W. are the main investigators of this study and participated in the conception and design of this study. R.L., H.Z., Q.L., G.Y., Y.Z., R.Y., H.W., C.W., Y.H., W.W. and X.Y. participated in patient recruitment and data collection. R.L. participated in the data analysis and interpretation, as well as the writing and revision of the paper. All authors have read the final version of this article and have agreed to publish it.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2024.04.004.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249. doi:10.3322/caac.21660.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72:7–33. doi:10.3322/caac.21708.
3. Barclay ME, Abel GA, Greenberg DC, Rous B, Lyratzopoulos G. Socio-demographic variation in stage at diagnosis of breast, bladder, colon, endometrial, lung, melanoma, prostate, rectal, renal and ovarian cancer in England and its population impact. *Br J Cancer*. 2021;124:1320–1329. doi:10.1038/s41416-021-01279-z.
4. Armstrong DK, Alvarez RD, Backes FJ, et al. NCCN Guidelines® insights: ovarian cancer, version 3.2022. *J Natl Compr Canc Netw*. 2022;20:972–980. doi:10.6004/jnccn.2022.0047.

5. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med*. 1995;332:1004–1014. doi:10.1056/NEJM199504133321507.
6. Weiss RB, Donehower RC, Wiernik PH, et al. Hypersensitivity reactions from taxol. *J Clin Oncol*. 1990;8:1263–1268. doi:10.1200/JCO.1990.8.7.1263.
7. Koudelka S, Turánek J. Liposomal paclitaxel formulations. *J Control Release*. 2012;163:322–334. doi:10.1016/j.jconrel.2012.09.006.
8. Cabanes A, Briggs KE, Gokhale PC, Treat JA, Rahman A. Comparative in vivo studies with paclitaxel and liposome-encapsulated paclitaxel. *Int J Oncol*. 1998;12:1035–1040. doi:10.3892/ijo.12.5.1035.
9. Sharma A, Mayhew E, Straubinger RM. Antitumor effect of taxol-containing liposomes in a taxol-resistant murine tumor model. *Cancer Res*. 1993;53:5877–5881.
10. Bi Z, Chen P, Liu YB, et al. Efficacy and safety analysis of paclitaxel, docetaxel and liposomal paclitaxel after neoadjuvant therapy in breast cancer. *Breast Cancer Res Treat*. 2020;184:397–405. doi:10.1007/s10549-020-05851-8.
11. Zhang J, Pan Y, Shi Q, et al. Paclitaxel liposome for injection (Lipusu) plus cisplatin versus gemcitabine plus cisplatin in the first-line treatment of locally advanced or metastatic lung squamous cell carcinoma: a multicenter, randomized, open-label, parallel controlled clinical study. *Cancer Commun*. 2022;42:3–16. doi:10.1002/cac2.12225.
12. Zeng J, Cui X, Cheng L, Chen Y, Du X, Sheng L. Liposome-paclitaxel and carboplatin combination chemoradiotherapy for patients with locally advanced esophageal squamous cell carcinoma. *Cancer Radiother*. 2021;25:441–446. doi:10.1016/j.canrad.2021.01.008.
13. Han G, Shi J, Mi L, et al. Clinical efficacy and safety of paclitaxel liposomes as first-line chemotherapy in advanced gastric cancer. *Future Oncol*. 2019;15:1617–1627. doi:10.2217/fon-2018-0439.
14. Liu SL, Sun XS, Li XY, et al. Liposomal paclitaxel versus docetaxel in induction chemotherapy using Taxanes, cisplatin and 5-fluorouracil for locally advanced nasopharyngeal carcinoma. *BMC Cancer*. 2018;18:1279. doi:10.1186/s12885-018-5192-x.
15. Fubin Z, Lining C, Kejun X. Comparison of efficacy and toxicities of paclitaxel liposome and traditional paclitaxel combined with carboplatin in the treatment of ovarian cancer. *Chinese Gen Pract*. 2017;15:808–810.
16. Haiyan C, Xiuwei C. A comparison of paclitaxel liposome and paclitaxel in the treatment for 100 cases with ovarian cancer. *China Cancer*. 2008;17:723–725.
17. Jia L, Yun L, Yongxiu Y, Xiaohui W. Effectiveness and safety of paclitaxel liposomes and carboplatin for ovarian cancer: a systematic review. *Chinese J Evid-Based Med*. 2012;12:42–48.
18. Wenjie H, Jianying X, Chi C, Min M, Yueming Z, Youguo C. Comparison of efficacy and safety between liposome-paclitaxel plus carboplatin and paclitaxel plus carboplatin on epithelial ovarian cancer. *Cancer Res Prevent Treat*. 2018;45:410–413.
19. Baozhuang W, Guangxing M. Efficacy and safety of paclitaxel and its liposome in the treatment of ovarian cancer: a meta−analysis. *China Pharmaceut*. 2019;28:73–78.
20. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2014;15:396–405. doi:10.1016/s1470-2045(14)70049-x.
21. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2003;21:3194–3200. doi:10.1200/JCO.2003.02.153.
22. Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal cancer treatment (ICON8): overall survival results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2022;23:919–930. doi:10.1016/S1470-2045(22)00283-2.
23. Clamp AR, James EC, McNeish IA, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *Lancet*. 2019;394:2084–2095. doi:10.1016/S0140-6736(19)32259-7.
24. Bernabeu E, Cagel M, Lagomarsino E, Moretton M, Chiappetta DA. Paclitaxel: what has been done and the challenges remain ahead. *Int J Pharm*. 2017;526:474–495. doi:10.1016/j.ijpharm.2017.05.016.
25. Yafeng Z. Comparison of efficacy and toxic and side effects of paclitaxel liposome combined with carboplatin versus conventional paclitaxel combined with carboplatin in the treatment of advanced ovarian cancer. *Liuzhou Med*. 2010:63–65.
26. Windebank MDB AJ, de Groen PC. Potential neurotoxicity of the solvent vehicle for cyclosporine. *J Pharmacol Exp Ther*. 1994;268:1051–1056.
27. Ma XH, Guo K, Dong WL, Jiang J. [Efficacy and safety of paclitaxel liposomes compared to paclitaxel combined with platinum in concurrent chemoradiotherapy for unresectable cervical carcinoma: a meta-analysis]. *Zhonghua Zhong Liu Za Zhi*. 2021;43:1132–1139. doi:10.3760/cma.j.cn112152-20210422-00337.