Saudi Journal of Biological Sciences 25 (2018) 909–916

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Original article

Lobaplatin-based regimens outperform cisplatin for metastatic breast cancer after anthracyclines and taxanes treatment

Zhipeng Wang [a,1], Lei Xu [b,1], Han Wang [c], Zhenzhi Li [d], Lu Lu [a], Xiaojia Li [a], Qingyuan Zhang [e,*]

[a] Department of Medical Oncology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin 150081, China
[b] Genetics Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA
[c] Department of Maternal and Child Health, School of Public Health, Peking University, Beijing 100191, China
[d] Department of Biochemistry and Molecular & Cellular Biology, Georgetown University Medical Center, Washington, DC 20057, USA
[e] Department of Medical Oncology, Tumor Hospital of Harbin Medical University, Harbin 150081, China

ARTICLE INFO

Article history:
Received 7 December 2017
Revised 14 January 2018
Accepted 15 January 2018
Available online 31 January 2018

Keywords:
Lobaplatin
Metastatic
Breast cancer
Resistant
Cisplatin

ABSTRACT

The goal of this study was to assess the antitumor efficacy and safety of lobaplatin-based regimens as the second line of treatment in patients with metastatic breast cancer (MBC) resistant to anthracyclines and taxanes, compared with that of cisplatin-based regimens. During August 2012 to April 2015, 87 patients who received lobaplatin-based regimens or cisplatin-based regimens were included. Medical records of the patients noted that lobaplatin (30 mg/m^2) or cisplatin (25 mg/m^2), combined with another chemotherapeutic agent such as Gemcitabine (1000 mg/m^2) or Vinorelbine (25 mg/m^2), was intravenously given to the patients on a basis of twenty-one days as one treatment cycle. All the patients were followed until August 2017. The endpoint of this study was progression-free survival (PFS), overall survival (OS), and estimated objective response rate (RR). Safety and drug tolerability data were also obtained. Lobaplatin-based regimens prolonged PFS compared to cisplatin-based regimens (median 13.2 vs 4.7 months, hazard ratio = 0.37, 95% confidence intervals: 0.21–0.67, $P = .0007$), while OS was not significantly different between the two groups (hazard ratio = 0.72, 95% confidence intervals: 0.40–1.30, $P = .2767$), as was objective RR (37.8% vs 33.4%, $x^2 = 0.19$, $P = .6653$). Nausea/vomiting and renal injury were more frequent with cisplatin-based regimens. Our results show that lobaplatin-based regimens are superior to cisplatin in terms of efficacy and are better tolerated.

1. Introduction

Breast cancer is by far the most frequent cancer in women (30% of all cancers), contributing to approximately 14% of all cancer-related mortalities (Akram et al., 2017; Siegel et al., 2017).

Even though polychemotherapy including anthracyclines and taxanes has been demonstrated to improve clinical outcomes, a substantial proportion of breast cancer patients still ultimately experience a relapse of metastatic disease (Sheri and Johnston, 2013; Clark et al., 2014; Zhou et al., 2015; Carrasco et al., 2016; Xu et al., 2016). After metastatic or adjuvant treatment, resistance to these agents is a limiting factor in breast cancer chemotherapy, especially for patients of Asian descent who often present with advanced disease (Andreopoulou and Sparano, 2013; Aogi et al., 2013; Deng et al., 2013; Xu et al., 2016; Wu et al., 2016; Reeder-Hayes and Anderson, 2017). With the increasing use of anthracyclines and taxanes for early breast cancer, fewer effective treatment options are available for patients (Valero and Hortobagyi, 2003;

Abbreviations: metastatic breast cancer, MBC; lobaplatin and gemcitabine, GL; lobaplatin and vinorelbine, NL; cisplatin and gemcitabine, GP; cisplatin and vinorelbine, NP; progression-free survival, PFS; overall survival, OS; response rate, RR; platinum-based compounds, PBCs; Eastern Cooperative Oncology Group, ECOG; performance scale, PS; granulocyte-colony stimulating factor, G-CSF; Response Evaluation Criteria in Solid Tumors, RECIST; National Cancer Institute Common Toxicity Criteria for Adverse Events, NCI-CTCAE; complete response, CR; partial response, PR; stable disease, SD; progressive disease, PD; lymph nodes, LN; estrogen receptor, ER; progesterone receptor, PR; human epidermal growth factor receptor 2, HER-2; triple negative breast cancer, TNBC; time to progression, TTP; non-small-cell lung cancer, NSCLC; hazard ratio, HR; confidence interval, CI; standard error, SE.

* Corresponding author.
E-mail address: zhma19650210@126.com (Q. Zhang).
[1] Both authors contributed equally to this work.

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2018.01.011
1319-562X/

Bernard-Marty et al., 2004; Wu et al., 2010; Gamucci et al., 2014; Xu et al., 2016).

Gemcitabine or vinorelbine is considered for treatment based on multiple phase II studies for metastatic breast cancer (MBC) patients previously treated with anthracyclines and taxanes (Saji, 2013). However, there is an unmet need for effective and safe salvage treatments for chemotherapy-resistant, patients with MBC (Latipova et al., 2011; Coyne et al., 2013; Xu et al., 2013; Ghersi, et al., 2015). Clinical studies have shown that platinum-based compounds (PBCs) are available to patients with MBC who failed treatments containing anthracyclines and taxanes (Shamseddine and Farhat, 2011; Egger et al., 2017). Furthermore, preclinical or clinical data have also demonstrated synergistic antitumoral activity between PBCs and gemcitabine or vinorelbine (Heinemann et al., 2006; Shamseddine and Farhat 2011; Wang et al., 2017a, 2017b). Cisplatin mainly impacts solid tumors and continues to play a major role in medical oncology (Moncharmont et al., 2011); however, its clinical usefulness is limited by renal, neurological, and gastrointestinal toxicity (Rezaee et al., 2017). Accordingly, second- and third-generation platinum analogues with reduced toxicity and a better therapeutic index, such as lobaplatin, have been developed. Phase I and II clinical trials in the US, Australia, EU, Brazil, and South Africa have demonstrated the effectiveness of lobaplatin in treating various cancers, including relapsed ovarian cancer, esophageal, head and neck, breast, and small cell lung cancer (Deng et al., 2013; Long et al., 2014; Peng et al. 2015; Zhang et al., 2016; Cao et al., 2017; Du et al., 2017; Ke et al., 2017). In China, lobaplatin is approved for the treatment of chronic myelogenous leukemia, inoperable MBC, hepatocellular carcinoma, and lung cancer (Wu et al., 2010; Xie et al., 2012). Lobaplatin might also lead to significantly enhanced treatment of cholangio carcinoma and colorectal carcinoma (Wheate et al., 2010; Zhou et al., 2010; Dai et al., 2011; Wang et al., 2012).

To date, no standard chemotherapy regimen has been proved to be effective in the treatment of anthracycline- and taxane-resistant MBC. Although cisplatin-based chemotherapy has been proven to have a major clinical impact, the outcome of lobaplatin-based synergistic treatment has been poorly evaluated in patients with MBC, particularly in Asian patients. To determine if lobaplatin-based regimens are more effective and better tolerated compared to cisplatin-based regimens in patients with MBC after anthracycline and taxane treatment, in this study we examined the clinical outcome in our institution.

2. Patients and methods

2.1. Patients

We referred to medical records of the patients seen during the period August 2012 to April 2015, who were pathologically diagnosed with invasive ductal carcinoma and received curative surgery at Tumor Hospital of Harbin Medical University. To be eligible for this study, patients were required to meet all of the following inclusion criteria: (1) patients older than 18 years old; (2) cytologically or histologically proven, bidimensionally measurable or evaluable MBC; (3) previously received anthracycline and taxane treatment as adjuvant or first-line chemotherapy for MBC; (4) had not received more than one chemotherapy regimen for metastatic disease (unless with anthracycline and/or taxane); (5) A: adequate bone marrow (platelets $\geq 100 \times 109$ cells/L, absolute neutrophil count $\geq 1.5 \times 10^9$ cells/L, hemoglobin ≥ 10 g/dL); B: hepatic function (total bilirubin $\leq 2 \times$ the upper limit of normal, aspartate transaminase $\leq 3 \times$ the upper limit of normal or $\leq 5 \times$ the upper limit of normal if metastatic disease was present in the liver) and estimated creatinine clearance >50 mL/min; C: Eastern Cooperative Oncology Group (ECOG) performance scale (PS): 0–2. Unlimited previous hormone therapies were allowed in this study, and patients with HER2-positive may not have had previous trastuzumab therapy. Anthracycline and taxane resistance was defined as tumor progression during treatment or within three months of the last dose after the first-line metastatic setting, or recurrence within six months of the adjuvant therapy.

The information of chemotherapy regimens was obtained through the analysis of medical records. The lobaplatin group was defined as follows: patients who received lobaplatin (30 mg/m^2) on day one were intravenously treated with gemcitabine (1000 mg/m^2) on day one and day eight (GL) or vinorelbine (25 mg/m^2) on day one and day eight (NL). The cisplatin group was defined as follows: patients who received cisplatin-based regimens, some of whom were treated with gemcitabine (1000 mg/m^2) on day one and day eight plus cisplatin (25 mg/m^2) on day one through day three (GP), while the others were treated with vinorelbine (25 mg/m^2) on day one and day eight plus cisplatin (25 mg/m^2) on day one through day three (NP) on the same schedule. Antiemetics were given before chemotherapy on day one. Granulocyte-colony stimulating factor (G-CSF) was not used prophylactically to prevent granulocytopenia. Regardless of treatment regimen, twenty-one days was considered to be a treatment cycle. Patients who completed at least two cycles of chemotherapy were taken into account.

Data for efficacy and side effects were also collected from medical records, which had been evaluated after at least two cycles of chemotherapy according to the Response Evaluation Criteria in Solid Tumors (RECIST1.1) criteria and the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) (version 4.0). Treatment was not terminated until disease progression or unacceptable toxicity. Patients' symptoms were measured at baseline and before each treatment cycle. Complete patient histories, physical examinations, complete blood cell counts, and chemistries (aspartate aminotransferase, total bilirubin, creatinine, albumin, and calculated creatinine clearance) were performed at baseline. A chest X-ray was performed prior to each course of treatment and complete blood cell counts were repeated weekly. Radiological imaging such as roentgenograms, computed axial tomographic scans, or magnetic resonance imaging was performed at baseline and after every two cycles of therapy to assess tumor response. Patients who did not conform to the above conditions were excluded.

The study was approved by the Local Commission for Medical Ethics and Clinical Studies of Harbin Medical University.

2.2. Follow-up

All patients were followed-up once a quarter after treatment until August 2017 or death. The end points in this study were progression-free survival (PFS), overall survival (OS), estimation of the objective response rate (RR), and evaluation of adverse events. PFS was defined from the first day of treatment to clinical/radiological determination of progression, from the first day of treatment to death from any cause was defined as OS. The objective RR was defined as the rate of complete response (CR) + partial response (PR) > four weeks duration. In this study, deaths were all due to breast cancer.

2.3. Statistical analysis

Patient demographics, RR, and toxic effects were recorded using the chi-square (x^2) or T test. The survival curves were estimated using Kaplan-Meier product-limit method. The univariate and multivariate Cox proportional hazards models were used to calcu-

late the hazard ratio (HR) and their corresponding 95% confidence intervals (CI). Factors that showed individual prognostic value in univariate models were used to examine their joint prognostic value in a multivariate model (criteria: entry = 0.1, removal = 0.1). A two-tailed $P < .05$ was inferred as statistically significant. All analyses were conducted in SAS version 9.3 (SAS Institute Inc., North Carolina).

3. Results

3.1. Patient demographics

A total of 87 patients met the eligibility criteria. Patient characteristics are shown in Table 1. 50 is the median age of the patients receiving lobaplatin-based regimens vs 49 being the median age of patients receiving cisplatin-based regimens. ($P = .3599$). The majority of patients were postmenopausal (68.9% vs 50% $P = .0726$), and 26.7% vs 11.9% ($P = .0827$) of patients were triple negative. Triple negative breast cancers (TNBC) are defined by the absence of estrogen receptors (ER) and progesterone receptors (PR) and the absence of human epidermal growth factor receptor 2 (HER-2). In this study, 31.1% vs 38.1% ($P = .4934$) of patients had ≥ two metastatic sites, and 28.9% vs 31.0% ($P = .8336$) had received hormonal therapy. Because the cost of the HER-2 inhibition was too expensive, only a minority of women had received trastuzumab treatment (8.9% vs 7.1% $P = .7648$).

3.2. Clinical activity

The mean number of treatment cycles was four per patient. Among the 45 patients who received lobaplatin-based regimens, 24 were intravenously treated with GL (53.33%) and 21 were treated with NL (46.67%). Among the 42 patients who received cisplatin-based regimens, 22 were treated with GP (52.38%) and 20 were treated with NP (47.62%).

Lobaplatin-based regimens prolonged PFS comparing to cisplatin-based regimens (median 13.2 vs 4.7 months, HR = 0.37, 95% CI: 0.21–0.67, $P = .0007$). After adjusting lymph nodes (LN) transfer, ER, PR, HER-2, P53, and number of sites of disease, lobaplation-based regimens still had a better PFS than cisplatin-based regimens (HR = 0.29, 95% CI: 0.15–0.56). The Kaplan–Meier curves for PFS are shown in Fig. 1. In contrast, the median OS was not significantly different between the two regimens (HR = 0.72, 95% CI: 0.40–1.30, $P = .2767$), as shown in Fig. 2. In GL/NL the median PFS for patients with TNBC and without TNBC was 8.0 months and 14.2 months, respectively ($x^2 = 2.42$, $P = .1197$) (Fig. 3), while a prolonged OS was found in non-TN relative to TN in GL/NL ($x^2 = 4.41$, $P = .0357$) (Fig. 4).

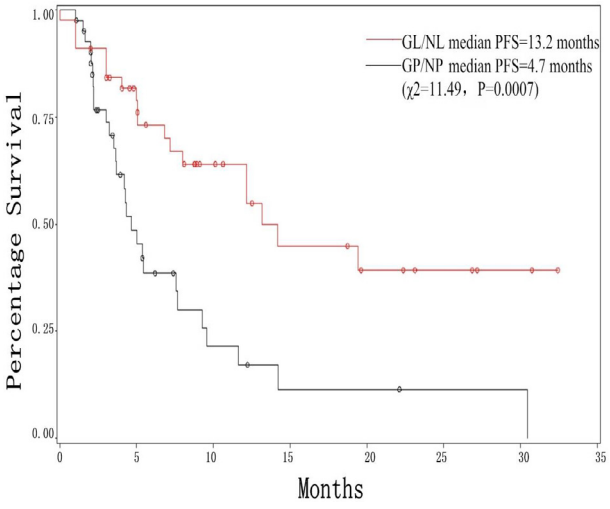

Fig. 1. Kaplan-Meier curves for PFS between GL/NL and GP/NP.

Table 1
Baseline patient demographics and disease characteristics.

Characteristic	Lobaplatin-based regimens		Cisplatin-based regimens		χ^2/T	P
	No. of Patients	%	No. of Patients	%		
Age, year					−0.92	.3599
Median	50		49			
Range	28–74		30–63			
Menopausal status					3.22	.0726
Pre-menopausal	14	31.1	21	50		
Post-menopausal	31	68.9	21	50		
ECOG scale					3.7	.157
0	11	24.4	9	21.4		
1	22	48.9	28	66.7		
2	12	26.7	5	11.9		
Hormone receptor status					2.03	.1541
ER and/or PR positive	21	46.7	16	38.1		
Triple negative	12	26.7	5	11.9	3.01	.0827
HER-2-positive	20	44.4	20	47.6	0.09	.7665
Clinical stages					0.84	.3603
III	15	33.3	18	42.9		
IV	30	66.7	24	57.1		
Site of metastatic disease					0.36	.5479
Visceral metastasis	20	44.4	16	38.1		
Other metastasis	25	55.6	26	61.9		
Extent of disease (No. of disease sites)					0.47	.4934
1	31	68.9	26	61.9		
≥2	14	31.1	16	38.1		
Trastuzumab (metastatic setting)	4	8.9	3	7.1	0.09	.7648
Hormonal therapy	13	28.9	13	31	0.04	.8336
Radiotherapy	13	28.9	10	23.8	0.29	.5914

ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; PR: progesterone receptor; HER-2:human epidermal growth factor receptor; Triple negative: ER negative; PR negative; HER-2 negative.

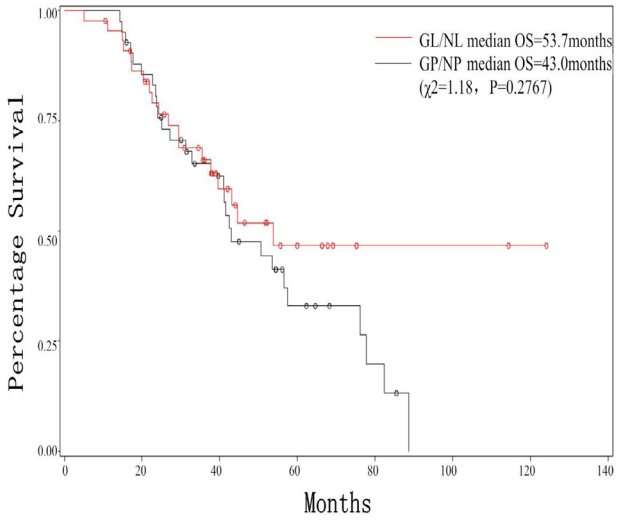

Fig. 2. Kaplan-Meier curves for OS between GL/NL and GP/NP.

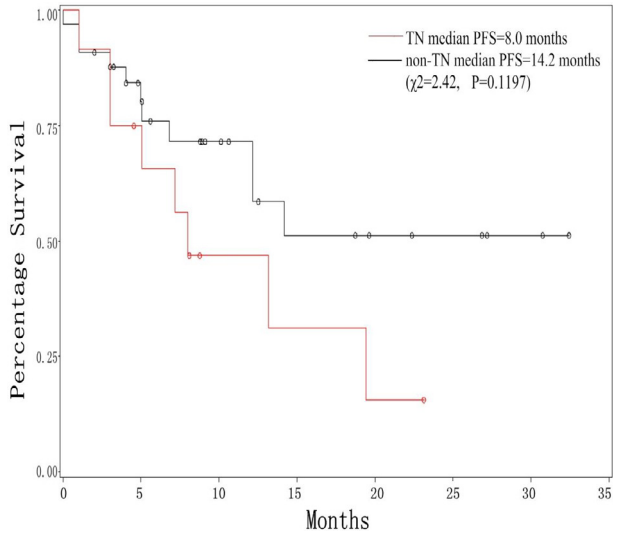

Fig. 3. Kaplan-Meier curves for PFS between TN and non-TN in GL/NL.

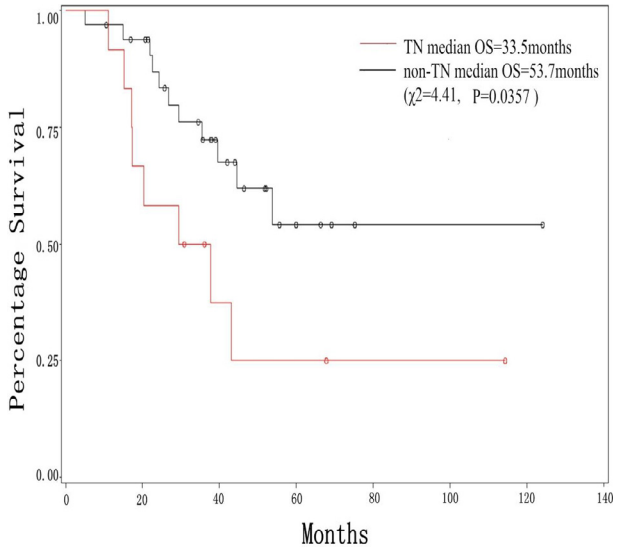

Fig. 4. Kaplan-Meier curves for OS between TN and non-TN in GL/NL.

In the subgroup analysis, based on treatment assignment, patients who received NL had a better PFS than patients who received NP treatment (x^2 = 14.19, P = .0002). While for OS, there was no significant difference between the two subgroups (x^2 = 1.625, P = .2024). When comparing GL with GP, there was no significant difference between GL and GP for PFS (x^2 = 3.3415, P = .0676) and OS (x^2 = 0.1496, P = .6989).

For the clinical pathological characteristics, high LN transfer rates, number of sites of disease (≥2), ER negative status, visceral metastases, and TNM stage IV were significantly associated with worse PFS in the univariate model (Table 2). Patients with HER-2 and P53 negative had a significantly prolonged PFS. In the multivariate model, the high LN transfer rates, number of sites of disease (≥2), ER negative status, and PR negative status were significantly associated with worse PFS (Table 3). In line with that of the univariate analysis, the results of the multivariate analysis revealed the same protective factors for PFS.

As for the OS of MBC, high LN transfer rates, presence of visceral metastases, ER negative, number of sites of disease (≥2), and TNM stage IV were significantly associated with worse OS in the univariate model (Table 4). Patients with HER-2 and P53 negative had a significantly prolonged OS. In the multivariate model, high LN transfer rates, presence of visceral metastases, and ER negative were significantly associated with worse OS (Table 5). Patients with HER-2 negative had a significantly prolonged OS.

In GL/NL, two patients (4.5%) achieved a CR and 15 (33.3%) achieved a PR, for an overall objective RR of 37.8%. Another 28.9% of patients had stable disease (SD) and 33.3% of patients had progressive disease (PD). In GP/NP, one patient (2.4%) achieved a CR and 13 (31.0%) achieved a PR, for an overall objective RR of 33.4%, while another 21.4% of patients had SD and 45.2% of patients had PD. The objective RR were similar between the two groups (37.8% vs 33.4%; x^2 = 0.19, P = .6653) (Table 6).

3.3. Adverse events

Treatment-related adverse events were mostly grade 1/2 and were generally reversible (Table 7). Myelosuppression and gastrointestinal reactions were the main side effects. Comparing lobaplatin-based regimens with cisplatin-based regimens, there was no statistically significant difference between them regarding grade 3/4 treatment-related absolute neutrophil count nadir values (15.55% vs 14.29%), grade 3/4 thrombocytopenia (8.89% vs 11.9%), or grade 3/4 anemia (4.44% vs 2.38%). Only 3.45% of patients required packed red blood cell transfusions. Nausea and vomiting in patients subjected to cisplatin-based regimens were significantly higher than those subjected to lobaplatin-based regimens (P = .0298), as was renal injury (P = .0341). Other mild toxicities including liver dysfunction and peripheral neurotoxicity were commonly noticed in both regimens during the course of treatment.

4. Discussion

The exploration of novel and effective chemotherapeutic combinations represents one of the major challenges in the palliative treatment of MBC (Pectasides et al., 2003; Shafei et al., 2017). Lobaplatin is a third-generation platinum complex with DNA-alkylating activity, which is more active and tolerable against cancer in combination with other drugs (McKeage, 2001). We demonstrate here that platinum treatments combined with gemcitabine or vinorelbine have good synergistic antitumoral activity in patients with MBC, especially in the lobaplatin group. To the best of our knowledge, none of the other studies mentioned above reported any data about lobaplatin. However, our analysis of the cisplatin group is verified by many other trials *in vivo* and *in vitro*. Both lobaplatin

Table 2
Univariate Cox model analysis for PFS.

Variable	Estimate	SE	Chi-Sq	*P*	HR	HR (95% CI)
Treatment assignment	−0.99	0.30	10.60	***.00***	0.37	0.21–0.67
Age	0.00	0.02	0.04	.84	1.00	0.97–1.03
Menopausal status	−0.05	0.30	0.03	.87	0.95	0.53–1.72
LN transfer rates	1.34	0.41	10.89	***.00***	3.81	1.72–8.42
ER	0.85	0.32	7.07	***.01***	2.35	1.25–4.40
PR	0.47	0.31	2.34	.13	1.61	0.88–2.95
HER-2	−0.71	0.30	5.59	***.02***	0.49	0.27–0.88
P53	−0.63	0.29	4.62	***.03***	0.53	0.30–0.94
Neoadjuvant	0.55	0.36	2.33	.13	1.74	0.86–3.53
PS	−0.05	0.20	0.05	.82	0.96	0.64–1.43
TNM	0.65	0.32	4.06	***.04***	1.92	1.02–3.63
Hormonal therapy	−0.37	0.33	1.30	.25	0.69	0.36–1.31
Trastuzumab	−0.10	0.60	0.03	.87	0.91	0.28–2.92
Number of sites of disease	0.90	0.30	8.77	***.00***	2.45	1.36–4.44
Visceral metastasis	0.67	0.30	4.97	***.03***	1.95	1.08–3.51

SE: standard error; HR: hazard ratio; CI: confidence interval.
HR favors the addition of lobaplatin-based therapy in clinically relevant patient factors.
An HR < 1 indicates a better outcome for the PFS within each prognostic factor.

Table 3
Multivariate Cox model analysis for PFS.

Variable	Estimate	SE	Chi-Sq	*P*	HR	HR (95% CI)
Treatment assignment	−1.24	0.34	13.45	***.00***	0.29	0.15–0.56
LN transfer	1.44	0.45	10.42	***.00***	4.23	1.76–10.15
ER	0.90	0.36	6.31	***.01***	2.47	1.22–4.98
PR	0.66	0.37	3.13	***.08***	1.93	0.93–4.00
HER-2	−0.85	0.32	6.91	***.01***	0.43	0.23–0.81
P53	−0.94	0.32	8.48	***.00***	0.39	0.21–0.74
Number of sites of disease	1.09	0.33	10.52	***.00***	2.96	1.54–5.70

SE: standard error; HR: hazard ratio; CI: confidence interval.
HR favors the addition of lobaplatin-based therapy in clinically relevant patient factors.
An HR < 1 indicates a better outcome for the PFS within each prognostic factor.

Table 4
Univariate Cox model analysis for OS.

Variable	Estimate	SE	Chi-Sq	*P*	HR	HR (95% CI)
Treatment assignment	−0.32	0.3	1.17	.28	0.72	0.40–1.30
Age	0.02	0.02	0.89	.35	1.02	0.98–1.05
Menopausal status	0.18	0.3	0.35	.55	1.2	0.66–2.16
LN transfer rates	1.56	0.42	13.63	***0***	4.76	2.08–10.90
ER	0.86	0.32	7.14	***.01***	2.36	1.26–4.42
PR	0.46	0.31	2.27	.13	1.58	0.87–2.88
HER-2	−0.61	0.3	4.28	***.04***	0.54	0.30–0.97
Ki67	0.35	0.32	1.19	.27	1.42	0.76–2.64
P53	−0.62	0.3	4.16	***.04***	0.54	0.30–0.98
TNM	0.58	0.32	3.32	***0.07***	1.79	0.96–3.36
Hormonal therapy	−0.49	0.33	2.2	.14	0.61	0.32–1.17
Trastuzumab	−0.14	0.6	0.05	.82	0.87	0.27–2.82
Number of sites of disease	0.63	0.3	4.59	***.03***	1.89	1.06–3.37
Visceral metastasis	0.88	0.3	8.79	***0***	2.42	1.35–4.35

SE: standard error; HR: hazard ratio; CI: confidence interval.
An HR < 1 indicates a better outcome for the OS within each prognostic factor.

Table 5
Multivariate Cox model analysis for OS.

Variable	Estimate	SE	Chi-Sq	*P*	HR	HR (95% CI)
LN transfer rates	2.18	0.46	22.11	***<.0001***	8.8	3.57–22.03
ER	1.25	0.36	11.74	***.00***	3.49	1.71–7.13
HER-2	−0.58	0.34	2.98	***.08***	0.56	0.29–1.08
Visceral metastasis	1.25	0.33	14.41	***.00***	3.50	1.83–6.67

SE: standard error; HR: hazard ratio; CI: confidence interval.
An HR < 1 indicates a better outcome for the OS within each prognostic factor.

Table 6
Objective tumor responses data.

Response	Lobaplatin-based regimens (n = 45)		Cisplatin-based regimens (n = 42)		χ^2	*P*
	No. of Patients	%	No. of Patients	%		
Objective response rate	17	37.8	14	33.4	0.19	.6653
Complete response (CR)	2	4.5	1	2.4		
Partial response (PR)	15	33.3	13	31.0		
Stable disease (SD)	13	28.9	9	21.4		
Progressive disease (PD)	15	33.3	19	45.2		

Table 7
Treatment-related adverse events.

Type	Lobaplatin-based regimens(n = 45) Grade					Cisplatin-based regimens(n = 42) Grade					χ^2	*P*
	0	1	2	3	4	0	1	2	3	4		
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)		
Neutropenia	23 (51.12)	9 (20)	6 (13.33)	5 (11.11)	2 (4.44)	24 (57.14)	8 (19.05)	4 (9.52)	6 (14.29)	0	2.47	.6499
Thrombocytopnia	30 (66.66)	8 (17.78)	3 (6.67)	4 (8.89)	0	30 (71.43)	4 (9.52)	3 (7.14)	5 (11.91)	0	1.34	.719
Anemia	34 (75.56)	5 (11.11)	4 (8.89)	2 (4.44)	0	33 (78.57)	5 (11.91)	3 (7.14)	1 (2.38)	0	0.39	.9427
Nausea and vomit	32 (71.11)	7 (15.56)	5 (11.11)	1 (2.22)	0	17 (40.488	14 (33.33)	7 (16.67)	4 (9.52)	0	8.97	.0298
diarrhea	40 (88.89)	4 (8.89)	1 (2.22)	0	0	34 (80.95)	5 (11.91)	3 (7.14)	0	0	1.5	.4733
liver dysfunction	41 (91.11)	4 (8.89)	0	0	0	38 (90.48)	2 (4.76)	2 (4.76)	0	0	2.68	.2618
Peripheral neurotoxicity	41 (91.11)	4 (8.89)	0	0	0	33 (78.57)	6 (14.29)	3 (7.14)	0	0	4.17	.1245
fatigue	28 (62.22)	9 (20)	8 (17.78)	0	0	22 (52.38)	11 (26.1)	9 (21.43)	0	0	0.88	.6452
renal injury	44 (97.78)	1 (2.22)	0	0	0	34 (80.95)	6 (14.29)	2 (4.76)	0	0	6.76	.0341

and cisplatin are bifunctional DNA cross-linking agents, leading to DNA damage and thereafter activating DNA repair polymerases. Inhibition of the repair of platinum-induced DNA lesions plays a critical role in gemcitabine-related cytotoxic synergism with platinum-based treatments (Achanta et al., 2001; Alli et al., 2011; Kawaguchi et al., 2014). The addition of gemcitabine to the platinum treatments results in significant clinical benefit and RR in MBC (Li and Russell, 2004; Gligorov et al., 2007; Wang et al., 2017a, 2017b; Zheng et al., 2017). When combined with platinum treatments, vinorelbine was also active and well tolerated in anthracycline- and taxane-pretreated patients with MBC (Li et al., 2015).

Despite a striking improvement in PFS, the addition of lobaplatin did not prolong OS in this study. From the first day of treatment to death from any cause was defined as OS. The factors that affect the OS are the most complex in clinical studies, including the patient's own factors, other medical factors, etc. These factors can interfere with the results of clinical research. Data on treatment administered after progression were not collected in this trial, precluding an exploratory analysis of the influence of subsequent therapy on OS. Although the median OS was not significantly different between the two regimens, PFS as a clinical study endpoint is a good indicator. There are fewer factors that affect PFS. The results of PFS are closely related to this study. The magnitude of this benefit is clinically meaningful. Few lobaplatin-based combination regimens have been evaluated in MBC. To test the eligibility of our study, we compared the results from the cisplatin arm of this study with those reported by other trials. In Phase II trials of GP, this combination of chemotherapy has been proven active with a median RR of 43.5% (range, 26–82%), and with a median time to progression (TTP) from 3.5 to 11.2 months (Chitapanarux et al., 2006). Five other studies on GP also demonstrated similar results with median RRs of 43% (range, 26%–50%) (Heinemann 2002). When NP was evaluated as a second-line therapy in patients with MBC, the RR ranged between 25% and 61% and median TTP ranged from 2.8 to 8.7 months (Shamseddine and Farhat, 2011). Results from our study are consistent with those reported by other trials in which GP/NP was the comparator. Furthermore, by a Cox proportional hazards model consistent clinical benefit in favor of lobaplatin-based therapy was maintained across baseline prognostic factors. Sensitivity analyses of potential confounding factors confirmed the robustness of the endpoint. According to our research, subgroup analysis based on treatment assignment is inappropriate because the samples of the subgroup are so few. Results from subgroup study may lack representativeness.

In our observation, most lobaplatin-related toxic effects were minimal, rare, limited, and had no detrimental effects on overall quality of life. This study shows that myelosuppression is the main dose-limiting toxicity of lobaplatin, but its degree is mild. Jan Welink *et al.* reported the same result (Welink et al., 1999). A phase I study of lobaplatin also found that thrombocytopenia was dose-limiting; its degree was related to dose and creatinine clearance at the time of drug administration (Gietema et al., 1993). The proper dose of lobaplatin needs further study. We confirmed that the hematologic toxicity of lobaplatin is not worse than that of cisplatin. G-CSF appears to improve the tolerance. On the contrary, we found cisplatin-based treatments were prone to more deleterious effects. The many other clinical analyses on treatment-associated hematologic toxicities derived from GP or NP combinations revealed worse side effects than those from our trials (Egger et al., 2017). Chitapanarux (Chitapanarux et al., 2006) reported that GP-related Grade 3/4 neutropenia occurred in 37% and grade 3/4 thrombocytopenia was seen in 17% of patients. In a study by Nagourney and colleagues (Nagourney et al., 2000), the GP-related grade 3/4 thrombocytopenia is 31%. Vassilomanolakis' group (Vassilomanolakis et al., 2003) reported that neutropenia grade 3/4 accounts for the major toxicity in NP (47%). These discrepancies of toxicity incidences are probably due to the differences in treatment schedules and different patient populations. The clinical administration of cisplatin is also limited by renal, neurological, and gastrointestinal toxicity (Rezaee et al., 2017). Our study demonstrated GL/NL-related nausea, vomiting, and renal injury are better tolerated than GP/NP-related adverse events. Incidences of peripheral neurotoxicity were similar in both groups. In light of the potential effects and side effects of this combination, we suggest using lobaplatin instead of cisplatin.

While tremendous improvement has been made for the treatment of breast cancers, the treatment of TNBC still remains a chal-

lenge due to its aggressive characteristics and limited treatment options (Wang et al., 2017a, 2017b). TNBC remains ominous and is associated with poor DFS and OS compared to non-TNBC (Lee and Djamgoz, 2017). PBCs achieved increased RR for TNBC, which had a significantly longer PFS than non-TN and a trend towards improved OS in metastatic disease (Sirohi et al., 2008; Guan et al., 2015). We did not observe an improved outcome for patients with metastatic TNBC compared to non-TNBC when treated with lobaplatin-based regimens. Possibly this is because of the low number of patients in this retrospective study; substantial differences between the patient populations of these studies may also account for the disparate results. Liu et al. (2013) reported that even though PBCs in the patients with breast cancer exhibiting TNBC showed an improved short-term efficacy compared with the non-TNBC group during neo-adjuvant chemotherapy, PBCs have not yet been demonstrated to have an improved effect in advanced breast cancer. Having a relatively smaller number of TNBC (n = 5) in GP/NP, our study did not analyze the cisplatin arm.

Some data demonstrates that the combination of lobaplatin with antitubulin agents might be a rational therapeutic strategy for human non-small-cell lung cancer (NSCLC), which is superior to that of cisplatin combined with antitubulin agents (Xie et al., 2012). Besides NSCLC, this study is the first to demonstrate that lobaplatin-based regimens are safer and offer more favorable PFS when compared with cisplatin-based regimens in the second line treatment of patients with MBC, a population with limited active treatment options. Therefore, the magnitude of this benefit is clinically meaningful.

These results have not been verified in multi-institutional trials; therefore, currently available evidence does not provide definitive guidance. Lobaplatin-based regimens deserve further investigation, which can also be used in the third or subsequent line setting. Future studies are needed in a larger patient population to evaluate efficacy and tolerability.

Acknowledgements

This experiment was finished in the oncology key lab of Heilongjiang Province Institution of Higher Education. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We thank the NIH Library Writing Center for manuscript editing assistance.

Ethical approval

Ethical approval was given by the Local Commission for Medical Ethics and Clinical Studies of Harbin Medical University.

Authors' contributions

Zhipeng Wang, Lei Xu, and Qingyuan Zhang designed the study and drafted the manuscript; Zhipeng Wang and Han Wang carried out the statistical analysis; Zhenzhi Li accomplished the interpretation of data; Zhipeng Wang, Lu Lu, and Xiaojia Li participated in collection of the samples. All authors read and approved the final manuscript.

References

Achanta, G. et al., 2001. Interaction of p53 and DNA-PK in response to nucleoside analogues: potential role as a sensor complex for DNA damage. Cancer Res. 61, 8723–8729.
Akram, M. et al., 2017. Awareness and current knowledge of breast cancer. Biol. Res. 50, 33.
Alli, E. et al., 2011. Enhanced sensitivity to cisplatin and gemcitabine in Brca1-deficient murine mammary epithelial cells. BMC Pharmacol. 11, 7.
Andreopoulou, E., Sparano, J.A., 2013. Chemotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer: an overview. Curr. Breast Cancer Rep. 5, 42–50.
Aogi, K. et al., 2013. Efficacy and safety of ixabepilone in taxane-resistant patients with metastatic breast cancer previously treated with anthracyclines: results of a phase II study in Japan. Cancer Chemother. Pharmacol. 71, 1427–1433.
Bernard-Marty, C. et al., 2004. Facts and controversies in systemic treatment of metastatic breast cancer. Oncologist 9, 617–632.
Cao, C.L. et al., 2017. Acute pancreatitis induced by etoposide-lobaplatin combination chemotherapy used for the treatment of lung cancer: a case report and literature review. Medicine (Baltimore). 96, e7601.
Carrasco, E. et al., 2016. Meroxest improves the prognosis of immunocompetent C57BL/6 mice with allografts of E0771 mouse breast tumor cells. Arch. Med. Sci. 12, 919–927.
Chitapanarux, I. et al., 2006. Gemcitabine plus cisplatin (GC): a salvage regimen for advanced breast cancer patients who have failed anthracycline and/or taxane therapy. Gan To Kagaku Ryoho. 33, 761–766.
Clark, O. et al., 2014. Targeted therapy in triple-negative metastatic breast cancer: a systematic review and meta-analysis. Core Evid. 9, 1–11.
Coyne, C.P. et al., 2013. Anti-neoplastic cytotoxicity of gemcitabine-(C4-amide)-[anti-HER2/neu] in combination with griseofulvin against chemotherapeutic-resistant mammary adenocarcinoma (SKBr-3). Med. Chem. (Los Angeles) 3, 210–223.
Dai, H.Y. et al., 2011. Lobaplatin suppresses proliferation and induces apoptosis in the human colorectal carcinoma cell Line LOVO in vitro. Biomed. Pharmacother. 65, 137–141.
Deng, Q.Q. et al., 2013. Phase II trial of Loubo(R) (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. Asian Pac. J. Cancer Prev. 14, 413–417.
Du, L. et al., 2017. Antitumor activity of Lobaplatin against esophageal squamous cell carcinoma through caspase-dependent apoptosis and increasing the Bax/Bcl-2 ratio. Biomed. Pharmacother. 95, 447–452.
Egger, S.J., et al., 2017. Platinum-containing regimens for metastatic breast cancer. Cochrane Database Syst. Rev. 6, CD003374.
Gamucci, T. et al., 2014. Eribulin mesylate in pretreated breast cancer patients: a multicenter retrospective observational study. J. Cancer. 5, 320–327.
Ghersi, D., et al., 2015. Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst. Rev. CD003366.
Gietema, J.A. et al., 1993. A phase I study of 1,2-diamminomethyl-cyclobutane-platinum (II)-lactate (D-19466; lobaplatin) administered daily for 5 days. Br. J. Cancer. 67, 396–401.
Gligorov, J., et al., 2007. [Updates on gemcitabine on metastatic breast cancer]. Bull. Cancer. 94 Spec No Actualites, S90–94.
Guan, X. et al., 2015. Platinum-based chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis of randomized-controlled trials. Anticancer Drugs. 26, 894–901.
Heinemann, V., 2002. Gemcitabine plus cisplatin for the treatment of metastatic breast cancer. Clin. Breast Cancer. 3 (Suppl 1), 24–29.
Heinemann, V. et al., 2006. High efficacy of gemcitabine and cisplatin in patients with predominantly anthracycline- and taxane-pretreated metastatic breast cancer. Cancer Chemother. Pharmacol. 57, 640–646.
Kawaguchi, H. et al., 2014. Gemcitabine as a molecular targeting agent that blocks the Akt cascade in platinum-resistant ovarian cancer. J. Ovarian Res. 7, 38.
Ke, L.R. et al., 2017. Safety and efficacy of lobaplatin combined with 5-fluorouracil as first-line induction chemotherapy followed by lobaplatin-radiotherapy in locally advanced nasopharyngeal carcinoma: preliminary results of a prospective phase II trial. BMC Cancer. 17, 134.
Latipova, D. et al., 2011. Role of gemcitabine in treatment of metastatic breast cancer. Vopr. Onkol. 57, 139–146.
Lee, A., Djamgoz, M.B.A., 2017. Triple negative breast cancer: emerging therapeutic modalities and novel combination therapies. Cancer Treat. Rev. 62, 110–122.
Li, H.C., Russell, C.A., 2004. Gemcitabine and platinum-based chemotherapy in metastatic breast cancer. Oncology (Williston Park). 18, 17–22.
Li, M. et al., 2015. Vinorelbine plus platinum in patients with metastatic triple negative breast cancer and prior anthracycline and taxane treatment. Medicine (Baltimore). 94, e1928.
Liu, M. et al., 2013. Platinum-based chemotherapy in triple-negative breast cancer: a meta-analysis. Oncol. Lett. 5, 983–991.
Long, G.X. et al., 2014. Single-arm, multi-centre phase II study of lobaplatin combined with docetaxel for recurrent and metastatic nasopharyngeal carcinoma patients. Oral Oncol. 50, 717–720.
McKeage, M.J., 2001. Lobaplatin: a new antitumour platinum drug. Expert Opin. Investig. Drugs. 10, 119–128.
Moncharmont, C. et al., 2011. Cisplatin or carboplatin, that is the question. Bull. Cancer. 98, 164–175.
Nagourney, R.A. et al., 2000. Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. J. Clin. Oncol. 18, 2245–2249.
Pectasides, D. et al., 2003. Oxaliplatin plus high-dose leucovorin and 5-fluorouracil in pretreated advanced breast cancer: a phase II study. Ann. Oncol. 14, 537–542.
Peng, Y. et al., 2015. A phase I clinical trial of dose escalation of lobaplatin in combination with fixed-dose docetaxel for the treatment of human solid tumours that had progressed following chemotherapy. Oncol. Lett. 9, 67–74.
Reeder-Hayes, K.E., Anderson, B.O., 2017. Breast cancer disparities at home and abroad: a review of the challenges and opportunities for system-level change. Clin. Cancer Res. 23, 2655–2664.

Rezaee, R. et al., 2017. Curcumin: a potentially powerful tool to reverse cisplatin-induced toxicity. Pharmacol. Res. 117, 218–227.
Saji, S., 2013. Evolving approaches to metastatic breast cancer patients pre-treated with anthracycline and taxane. BioDrugs 27, 469–478.
Shafei, A. et al., 2017. A review on the efficacy and toxicity of different doxorubicin nanoparticles for targeted therapy in metastatic breast cancer. Biomed. Pharmacother. 95, 1209–1218.
Shamseddine, A.I., Farhat, F.S., 2011. Platinum-based compounds for the treatment of metastatic breast cancer. Chemotherapy. 57, 468–487.
Sheri, A., Johnston, S., 2013. New developments and future directions in systemic therapy. Clin. Oncol. (R Coll Radiol) 25, 117–126.
Siegel, R.L. et al., 2017. Cancer Statistics, 2017. CA Cancer J. Clin. 67, 7–30.
Sirohi, B. et al., 2008. Platinum-based chemotherapy in triple-negative breast cancer. Ann. Oncol. 19, 1847–1852.
Valero, V., Hortobagyi, G.N., 2003. Are anthracycline-taxane regimens the new standard of care in the treatment of metastatic breast cancer? J. Clin. Oncol. 21, 959–962.
Vassilomanolakis, M. et al., 2003. Vinorelbine and cisplatin for metastatic breast cancer: a salvage regimen in patients progressing after docetaxel and anthracycline treatment. Cancer Invest. 21, 497–504.
Wang, C. et al., 2017a. Triple negative breast cancer in Asia: an insider's view. Cancer Treat. Rev. 62, 29–38.
Wang, J. et al., 2017b. Efficacy and safety of vinorelbine plus cisplatin vs. gemcitabine plus cisplatin for treatment of metastatic triple-negative breast cancer after failure with anthracyclines and taxanes. Med. Sci. Monit. 23, 4657–4664.
Wang, Z. et al., 2012. Lobaplatin induces apoptosis and arrests cell cycle progression in human cholangiocarcinoma cell line RBE. Biomed. Pharmacother. 66, 161–166.
Welink, J. et al., 1999. Pharmacokinetics and pharmacodynamics of lobaplatin (D-19466) in patients with advanced solid tumors, including patients with impaired renal of liver function. Clin. Cancer Res. 5, 2349–2358.
Wheate, N.J. et al., 2010. The status of platinum anticancer drugs in the clinic and in clinical trials. Dalton Trans. 39, 8113–8127.
Wu, Q. et al., 2010. Lobaplatin arrests cell cycle progression in human hepatocellular carcinoma cells. J. Hematol. Oncol. 3, 43.
Xie, C.Y. et al., 2012. Antitumor activity of lobaplatin alone or in combination with antitubulin agents in non-small-cell lung cancer. Anticancer Drugs. 23, 698–705.
Xu, L. et al., 2016. A meta-analysis of combination therapy versus single-agent therapy in anthracycline- and taxane-pretreated metastatic breast cancer: results from nine randomized Phase III trials. Onco Targets Ther. 9, 4061–4074.
Xu, Y.C. et al., 2013. A systematic review of vinorelbine for the treatment of breast cancer. Breast J. 19, 180–188.
Zhang, S. et al., 2016. An open-label, single-arm phase II clinical study of docetaxel plus lobaplatin for Chinese patients with pulmonary and hepatic metastasis of nasopharyngeal carcinoma. Anticancer Drugs. 27, 685–688.
Zhou, B. et al., 2010. Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. J. Vasc. Interv. Radiol. 21, 333–338.
Zhou, L.Y. et al., 2015. Potential role of pemetrexed in metastatic breast cancer patients pre-treated with anthracycline or taxane. Chronic Dis. Transl. Med. 1, 27–35.