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

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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/m²) or cisplatin (25 mg/m²), combined with another chemotherapeutic agent such as Gemcitabine (1000 mg/m²) or Vinorelbine (25 mg/m²), 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%, x² = 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.

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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 (Andreadouliou 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;
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 proved 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 ≥100 × 10^9 cells/L, absolute neutrophil count ≥1.5 × 10^9 cells/L, hemoglobin >10 g/dL); B: hepatic function (total bilirubin ≤2 × the upper limit of normal, aspartate transaminase ≤3 × the upper limit of normal or ≤5 × 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/m²) on day one were intravenously treated with gemcitabine (1000 mg/m²) on day one and day eight (GL) or vinorelbine (25 mg/m²) 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/m²) on day one and day eight plus cisplatin (25 mg/m²) on day one through day three (GP), while the others were treated with vinorelbine (25 mg/m²) on day one and day eight plus cisplatin (25 mg/m²) 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 ($\chi^2$) 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 $P < 0.05$ 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, lobaplatin-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).

Table 1
Baseline patient demographics and disease characteristics.

| Characteristic                        | Lobaplatin-based regimens | Cisplatin-based regimens | $\chi^2$/$T$ | $P$     |
|---------------------------------------|---------------------------|--------------------------|--------------|---------|
| Age, year (No. of Patients, %)        |                           |                          |              |         |
| Median                                | 50                        | 49                       | -0.92        | .3599   |
| Range                                 | 28–74                     | 30–63                    |              |         |
| Menopausal status (No. of Patients, %)|                           |                          |              |         |
| Pre-menopausal                        | 14                        | 21                       | 3.22         | .0726   |
| Post-menopausal                       | 31                        | 50                       |              |         |
| ECOG scale (No. of Patients, %)       |                           |                          |              |         |
| 0                                     | 11                        | 9                        | 21.4         | 0.1941  |
| 1                                     | 22                        | 28                       | 66.7         | .4934   |
| 2                                     | 12                        | 5                        | 11.9         | .2157   |
| Hormone receptor status (No. of Patients, %) |                      |                          |              |         |
| ER and/or PR positive                 | 21                        | 16                       | 38.1         | .0027   |
| Triple negative                       | 12                        | 5                        | 11.9         | .0009   |
| HER-2-positive                        | 20                        | 20                       | 47.6         | .6865   |
| Clinical stages (No. of Patients, %)  |                           |                          |              |         |
| III                                   | 15                        | 18                       | 42.9         | .3603   |
| IV                                    | 30                        | 24                       | 57.1         | .5479   |
| Site of metastatic disease (No. of Patients, %) |                  |                          |              |         |
| Visceral metastasis                   | 20                        | 16                       | 38.1         | .0473   |
| Other metastasis                      | 25                        | 26                       | 61.9         | .4934   |
| Extent of disease (No. of disease sites) |                           |                          |              |         |
| 1                                     | 31                        | 26                       | 61.9         | .0473   |
| ≥2                                    | 14                        | 16                       | 38.1         | .2914   |
| Trastuzumab (metastatic setting)      | 4                         | 3                        | 7.1          | .09     |
| Hormonal therapy                      | 13                        | 13                       | 31           | .04     |
| Radiotherapy                          | 13                        | 10                       | 23.8         | .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.
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) |
|-------------------------------|----------|-----|--------|-----|-----|-------------|
| Treatments assignment        | −0.99    | 0.30| 10.60  | .00 | 0.37| 0.21–0.67   |
| Age                          | 0.00     | 0.02| 0.04   | .84 | 1.00|             |
| 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| 1.00–5.78   |
| PR                           | 0.47     | 0.31| 1.34   | .26 | 1.13| 0.78–1.64   |
| 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                           | 0.01     | 0.20| 0.05   | .82 | 0.96| 0.56–1.64   |
| TNM                          | 0.65     | 0.32| 4.06   | .04 | 1.92| 1.02–3.63   |
| 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) |
|---------------------------|----------|-----|--------|-----|-----|-------------|
| Treatments 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| 4.84   | .03 | 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) |
|---------------------------|----------|-----|--------|-----|-----|-------------|
| Treatments 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               | 1.56     | 0.42| 13.63  | .01 | 4.76| 2.08–10.90  |
| ER                        | 0.86     | 0.32| 7.14   | .03 | 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| 0.30–0.98   |
| Ki67                      | 0.35     | 0.32| 1.19   | .24 | 1.42| 0.76–2.64   |
| P53                       | −0.06    | 0.3 | 4.16   | .04 | 0.54| 0.30–0.98   |
| TNM                       | 0.58     | 0.32| 3.32   | .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| 1.06–3.73   |
| Visceral metastasis       | 0.88     | 0.3 | 8.79   | <.0001| 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               | 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.
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 MBC (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.

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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 MBC (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-
lengle 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 lobaratin-based regimens. Possibly this is because of the low number of patients in this retrospective study; substance 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 lobaratin 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 lobaratin-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. Lobaratin-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.

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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 Xiaoia Li participated in the collection of the samples. All authors read and approved the final manuscript.

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