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Original article

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/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.

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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-

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