RESEARCH ARTICLE

Phase II Trial of Loubo® (Lobaplatin) and Pemetrexed for Patients with Metastatic Breast Cancer not Responding to Anthracycline or Taxanes

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Abstract

Purpose: This phase II study was undertaken to determine the efficacy and safety of Loubo® (Lobaplatin) in combination with pemetrexed in treating patients with metastatic breast cancer who failed to respond to anthracycline or taxanes. Patients and Methods: Metastatic breast cancer cases who had previously received an anthracycline and a taxane in either adjuvant or metastatic settings, were enrolled. All patients were recruited from Jiangsu Cancer Hospital and Research Institute, and were treated with Loubo® (Lobaplatin) 35 mg/m² (intravenous; on day 1) and pemetrexed 500 mg/m² (intravenous; on day 1) every 21 days. Efficacy and side effects were evaluated after at least two cycles of chemotherapy. Results: All eligible 19 patients completed at least 2 cycles of chemotherapy with pemetrexed and lobaplatin, and were evaluable. Overall, 3 (15.8%) patients achieved partial response, 11 (57.9%) stable disease, 5 (26.3%) progression of disease, with no complete remission. Response rate was 15.8%, disease control rate was 42.1%. The median survival time was 10.3 months. Neutrophil suppression occurred in 36.8% of patients who had grade 2 toxicity, and 26.3% had grade 3, 26.4% had grade 4. Thrombocytopenia was encountered as follows: 21.1% grade 2, 15.8% grade 3 and 5.5% grade 4. Incidences of anemia were 10.5% in grade 2, 5.3% grade 3 and 0% grade 4. Only 5.3% of patients required packed red blood cell transfusion. Grade 3 digestive tract toxicity occurred in 5.5% of patients. Other toxicities included elevated transaminase,oral mucositis and skin rashes. Conclusions: The regimen of lobaplatin and pemetrexed is modestly active in metastatic breast cancer patients who failed anthracycline or taxanes, and the toxicity profile suggesting that the doses of chemotherapy should be further modified.

Keywords: Clinical trial - pemetrexed - lobaplatin - metastatic breast cancer

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Introduction

When single-agent chemotherapy was used in hormone-resistant metastatic setting, agents considered to be active include cyclophosphamide, phenylalanine mustard, vincristine, vinblastine, methotrexate and 5-fluorouracil. Response rates are ranged from 0-38% (M Akram et al., 2012). Presently, combined chemotherapy is mostly prescribed in neoadjuvant, adjuvant and in metastatic settings of breast cancer. Although CMF regimen represented the gold standard in the 1970s (Bonadonna et al., 1976), anthracycline-based regimens are the mainstay of adjuvant chemotherapy for early breast cancer since the 1990s (EBCTCG, 2005). The incorporation of a taxane into an anthracycline-based regimen demonstrated further benefit in the treatment of early-stage breast cancer. The Breast Cancer International Research Group 001 demonstrated superior disease-free survival and overall survival when docetaxel was given concurrently with doxorubicin and cyclophosphamide (TAC) compared with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) in breast cancer patients in advanced stages (Martin, 2005).However, it is still urgent to develop new regimens for patients who failed treatments containing taxanes or anthracyclines.

Pemetrexed is a novel multitargeted antifolate that inhibits several enzymes in the de novo pathways of pyrimidine and purine biosynthesis, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide ormyltransferase. Pemetrexed demonstrated activity in a variety of tumor types based on previous reports, including non-small cell lung cancer, malignant pleural mesothelioma, pancreas, colorectal, gastric, bladder, breast, and head and neck cancers (Martin,

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2006).

Lobaplatin is a platinum complex with DNA alkylating activity that was developed by ASTA Medica (Degussa). Cisplatin, one of the original platinum compounds, has a major impact on the treatment of solid tumors such as germ cell cancer, ovarian cancer, bladder cancer and bronchial carcinoma, but its clinical usefulness is limited by renal, neurological and gastrointestinal toxicity. This has led to the development of second- and third-generation platinum analogues, such as lobaplatin, with reduced toxicity and a better therapeutic index. Lobaplatin has been approved in China for the treatment of chronic myelogenous leukaemia (CML), inoperable metastatic breast and small cell lung cancer. Phase II clinical trials in the US, Australia, EU, Brazil and South Africa suggests the effectiveness of lobaplatin in the treatment for various cancers, including breast, oesophageal, lung and ovarian cancers as well as CML (Drugs, 2003).

Thus we conduct this phase II trail to test our hypothesis that pemetrexed combined with lobaplatin could be effective for patients with metastasis breast cancer who failed previous anthracycline or taxanes.

Materials and Methods

Patient selection

Women with histological or cytologic confirmed bidimensionally measurable breast cancer with clinical evidence of metastatic disease were eligible for this study. Other eligible criteria include: they previously received an anthracycline and a taxane or a combination of both, in the adjuvant or metastatic setting; have not received more than one chemotherapy regimen for metastatic disease (unless with a taxane and/or anthracycline); age ≥18 years; adequate bone marrow (platelets ≥ 100×10^9 cells/l, absolute neutrophil count ≥ 1.5×10^9 cells/l), hepatic (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 a life expectancy of ≥3 months; sign an informed consent before chemotherapy.

Exclusion criteria included: diagnosis of another malignancy within the past 5 years; uncontrolled infection or any chronic debilitating disease; clinically significant effusions (pericardial, pleural, ascites) unless these could be controlled; major surgery or any immunologic, genetic, radiation or chemotherapy < 4 weeks.

Methods

Loubo® (Lobaplatin, provided by Yibai Pharmaceutical Company) 35 mg/m^2 was given on day 1 and pemetrexed 500 mg/m^2 was also given on day 1 and repeated every 3-week; 400 μg of folic acid was given orally daily and 1000 μg of vitamin B12 was given intramuscularly every 9 weeks starting 7 days prior to the first dose and until 3 weeks after the last dose of pemetrexed; 4.5 mg of dexamethasone was given orally every 12 h on the day before, day of and the day after all doses of pemetrexed. Antiemetics were given before chemotherapy on days 1. Colony-stimulating factors were not used prophylactically to prevent granulocytopenia. Treatment continued until disease progression, unacceptable toxicity or two cycles beyond identification of a complete response (CR). All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0) (National Cancer Institute, 1998).

Clinical workup

Complete patient histories, physical examinations, complete blood cell counts, chemistries (aspartate aminotransferase, total bilirubin, creatinine, albumin), calculated creatinine clearance and chest X-ray were performed at baseline, with the exception of chest X-ray, prior to each course of treatment. Complete blood cell count was repeated weekly. Radiological studies (roentgenograms, computed axial tomographic scans or magnetic resonance imaging) were performed at baseline and after every two cycles of therapy to assess tumor response. CR was defined as complete disappearance of all measurable disease. Partial response (PR) was defined as at least 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. Progression was defined as 50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) or appearance of any new lesion, or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). Stable disease (SD) was documented when there was persistence of disease without meeting the criteria for progression, PR or CR.

Statistical design

Time to progression was defined as the time from registration to the date of progression. Survival was defined as the time from registration to death due to breast cancer. The distribution of time to progression and survival time was estimated using the Kaplan–Meier method.

Research Experience

We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

Patient demographics

A total of 19 patients were enrolled between August 2009 and April 2012. The majority of women were postmenopausal (78%) and had visceral metastasis (86%). Twelve (63%) had received prior hormonal therapy.

Clinical activity

All 19 patients completed at least 2 cycles of chemotherapy, and were evaluated according to study protocol. Overall, 3 (15.8%) patients achieved PR, 11 (57.9%) SD, 5 (26.3%) PD, RR was 15.8%, DCR 42.1%.

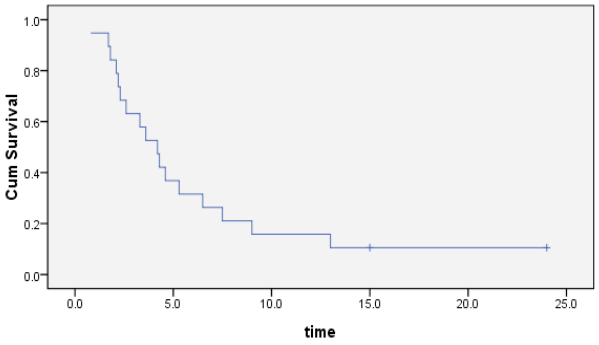

Figure 1. Kaplan–Meier Curves for Overall Survival

Table 1. Common Grade 1 to 4 Toxicities

Type	Grade 1(%)	Grade 2(%)	Grade 3(%)	Grade 4(%)
Neutropenia	2(10.5)	7(36.8)	5(26.3)	5(26.4)
Anemia	5(26..3)	2(10.5)	1(5.3)	0(0)
Thrombocytopenia	6(31.6)	4(21.1)	3(15.8)	1(5.5)
Elevated transaminase	3(15.8)	2(10.5)	0(0)	0(0)
Oral mucositis	1(5.3)	1(5.3)	0(0)	0(0)
Rash	1(5.3)	0(0)	0(0)	0(0)
Digestive tract reaction.	4(21.1)	3(15.8)	1(5.3)	0(0)

The follow-up ended in November 30, 2012. The median survival time was 10.3 months. The Kaplan–Meier curves for overall survival is shown in Figure 1.

Toxicity

Without prophylactic colony-stimulating factors support, 36.8% of patients had absolute neutrophil count nadir values constituting grade 2 toxicity, 26.3% had grade 3 toxicity, 26.4% had grade 4 toxicity. Thrombocytopenia was 21.1% in grade 2,15.8% in grade 3 and 5.5% in grade 4. Anemia occurred with incidences of 10.5% in grade 2, 5.3% in grade 3 and 0% in grade 4. Only 5.3% of patients required packed red blood cell transfusion. 5.5% of patients had digestive tract reaction of grade 3. Other toxicities include elevated transaminase, oral mucositis and skin rash. No neurological, renal and ototoxic adverse reaction was recorded (Table 1).

Discussion

Adjuvant systemic therapies for breast cancer have led to a significant reduction in the risk of relapse and improvement in overall survival. However, a substantial proportion of breast cancer patients still ultimately experience relapse with metastatic disease (Sheri et al., 2013). Several classes of cytotoxic agents, including anthracyclines and taxanes, are currently available to be used either singly or in combination. Combination chemotherapy regimens result in higher response rates; however, significant prolongation in overall survival is yet to be demonstrated. In addition,the increasing use of anthracyclines and taxanes in the adjuvant setting has limited further chemotherapy options in relapsed disease. The testing of novel agents and combinations in metastatic breast cancer, especially for tumors that were previously treated with anthracycline and taxane, is therefore warranted (Ma et al., 2006).

Pemetrexed has been tested in five phase II trials in locally advanced or metastatic breast cancer. The drug has shown an activity of around 30% in advanced breast cancer patients with minimal or no prior chemotherapy. In patients who received prior anthracyclines, response rates of 21% were reported. Responses have also been observed in a moderate proportion of patients who had been pretreated with anthracyclines, taxanes, and capecitabine. Some studies have suggested that a correlation exists between thymidylate synthase tumor expression with pemetrexed antitumor activity; this attractive hypothesis should be confirmed in further studies (Martin, 2006).

Robert NJ et al reported a subset analysis of a phase II study of pemetrexed as first-line chemotherapy in patients with advanced or metastatic breast cancer. Based on 35 evaluable patients,the overall response rate (ORR) was 26% (1 CR and 8 PR), and the clinical benefit rate (CR+ PR+ stable disease [SD] ≥ 6 months) was 40%. Median progression-free survival (PFS) was 4.1 months (range, <1-22.4). Median overall survival (OS) was 18.9 months (range, <1-27.7). Grades 3-4 treatment-related toxicities included: neutropenia (36%), leukopenia (17%), fatigue (14%), and anemia (14%). Grade 1/2 alopecia was seen in 8% of patients (Robert et al., 2011).

Garin A et al reported a subset analysis of a phase II study with pemetrexed and carboplatin in patients with locally advanced or metastatic breast cancer. Partial responses (RECIST criteria) were achieved in 27 (54.0%) patients (ORR = 54.0%; 95% CI, 39.3-68.2%). The median response duration was 11.1 months (95% CI, 6.5-14.0 months) and the median time to disease progression was 10.3 months (95% CI, 8.3-14.6 months). CTC hematologic toxicities were grade 3/4 neutropenia (58.0%/28.0%) and grade 3 thrombocytopenia (10.0%) and anemia (18.0%). Two (4.0%) patients had febrile neutropenia, 1 of whom died. No grade 4 non-hematologic toxicities occurred. Grade 3 non-hematologic toxicities were ALT (4.0%) and AST elevation, and edema, fatigue, pruritus, rash/desquamation, and renal toxicity (2.0% each) (Garin et al., 2008).

The main toxicities of the pemetrexed are myelosuppression, skin rash, and mucositis. Addition of folic acid and vitamin B12 significantly reduced the toxicity of pemetrexed, especially hematologic toxicity and gastrointestinal toxicity. Pemetrexed is the expected agent for use in high risk patients, especially elderly or poor performance status patients (Sudoh et al., 2008). Jan Welink et al reported that the dose-limiting toxicity of lobaplatin is thrombocytopenia. Hematological toxicity was considerable,and thrombocytopenia was the most prominent toxicity. Nadirs of blood counts were observed between days 14 and 16 after lobaplatin administration. The majority of patients experienced grade 4 thrombocytopenia (Jan Welink et al., 1999). A phase I study of lobaplatin found that thrombocytopenia was dose-limiting, its degree was related to dose and CRCL at time of drug administration. The recommended dose of lobaplatin i.v. bolus daily for 5 days for phase II studies depends on renal function, namely 30 $mg.m^{-2}$ at CRCL 60-80 $ml.min^{-1}$; 55 $mg.m^{-2}$ at CRCL 81-100 $ml.min^{-1}$; 70 $mg.m^{-2}$ at CRCL > 100 $ml.min^{-1}$ (Gietema et al., 1993). The dose of lobaplatin need a further study.

The main toxicity was myelosuppressionin in this trial.

3 To 4 grade neutropenia, and thrombocytopenia were 52.7% and 21.3% respectively. The count of leukocyte and platelet returned to normal after the treatment of colony-stimulating factor, interleukin 11 and recombinant human thrombopoietin. The high rate of myelosuppressionin considered for three line therapy and the drug toxicity of lobaplatin. Infection and bleeding should be attention to the application of lobaplatin.

In this study, digestive tract reaction ranged from 1 to 2 could be alleviated by symptomatic treatment. By hepatoprotective drugs, transaminase could return to normal. Only 2 patients had oral mucositis, with the supplements of vitamins and oral care, the oral mucosal healing with no fungal infection. 1 patient had rash with pruritus, rash subsided gradually after symptomatic treatment of the antipruritic and anti allergic.

In conclusion, our study provides another viable treatment option for patients with metastatic breast cancer who have been treated with anthracyclines and taxanes. Future studies using lower doses of lobaplatin and modification of administration schedules for the combination of pemetrexed and lobaplatin are needed in a larger patient population to evaluate the efficacy and tolerability.

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