Original Study

A Phase II Study of Lipoplatin (Liposomal Cisplatin)/Vinorelbine Combination in HER-2/neu–Negative Metastatic Breast Cancer

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Abstract

We assessed the efficacy and safety of a liposomal cisplatin (lipoplatin) and vinorelbine combination in metastatic breast cancer (MBC). Thirty-five patients were treated. The objective response rate was 53.1% and the median survival time was 22 months. Grade 3/4 neutropenia was observed in 44% of cycles, and febrile neutropenia was seen in 4 patients (11.4%). No grade 3/4 nephrotoxicity or neuropathy was noted. This combination is effective and well tolerated in patients with MBC and it warrants investigation as first-line treatment.

Background: Liposomal cisplatin (lipoplatin) has a mechanism of action similar to that of cisplatin, with reduced toxicities and enhanced or similar efficacy. We wanted to assess the efficacy and safety of a lipoplatin/vinorelbine combination in a phase II clinical trial in metastatic breast cancer (MBC). **Methods:** Thirty-five patients with HER-2/neu–negative (HER-2/neu$^-$) MBC were enrolled. Lipoplatin 120 mg/m^2 (days 1, 8, and 15) and vinorelbine 30 mg/m^2 (days 1 and 8) were administered in a 21-day cycle. **Results:** Thirty-five patients were included in the intent-to-treat (ITT) analysis; 32 patients were evaluable for response. The objective response rate was 53.1%. Complete response (CR) was achieved in 3 patients (9.4%), partial response (PR) was seen in 14 patients (43.8%), stable disease (SD) was obtained in 12 patients (37.5%), and progressive disease (PD) was seen in 3 patients (9.4%). Median time to disease progression was 8 months (range 6-10 months). After a median follow-up of 15.5 months, 18 patients were still alive; the median survival time was 22 months (95% confidence interval [CI], 14-30). A total of 174 cycles were administered. Neutropenia was the most frequent hematologic toxicity, with grade 3/4 neutropenia observed in 44% of cycles. Febrile neutropenia was observed in 4 patients (11.4%). No grade 3/4 nephrotoxicity or neuropathy was noted. Grade 1/2 nephrotoxicity occurred in 8 patients (22.9%) and grade 3 vomiting was seen in 3 patients (8.6%). **Conclusions:** The results of this trial reveal that vinorelbine/lipoplatin is effective in treating patients with MBC. This regimen is well tolerated with no grade 3/4 nephrotoxicity or neuropathy. The investigation of this regimen as first-line treatment in MBC is warranted.

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Introduction

Breast cancer is by far the most common cancer worldwide in women, composing about 23% of all cases of cancer in women.[1] Metastatic breast cancer (MBC) represents 10% of newly diagnosed patients with breast cancer. However a considerable number of patients with early or localized breast cancer will experience metastases along the course of their disease.[2]

MBC is generally considered to be incurable, and conventional cytotoxic chemotherapy is used mainly for palliation. The addition of anthracyclines and then taxanes to chemotherapy options has markedly improved the ability to treat MBC compared with previous regimens that consisted mainly of cyclophosphamide/methotrexate/5-fluorouracil combinations.[3]

The anthracyclines, consisting of doxorubicin and epirubicin, and the taxanes, consisting of paclitaxel and docetaxel, are the most active agents in MBC. Anthracycline-based regimens produced a 50%-75% response rate, with less than 15% complete response (CR) rate and a median survival range of 12-24 months.[4] The taxanes represent the standard therapy for MBC as first-line treatment or after failure of previous chemotherapy, in particular the anthracyclines.[5] Paclitaxel and docetaxel use as single agents in first-line therapy yielded overall response rates of 36%-62% and 52%-68%, respectively.[6] The addition of taxanes, in particular docetaxel, to anthracycline-based regimens yielded significantly higher response rates and longer time to progression (TTP) than anthracycline-based regimens alone in several phase III trials; however no advantage was reported in overall survival (OS).[7,8] Survival advantages, however, have been reported with the use of taxanes and gemcitabine or capecitabine in patients with MBC pretreated with anthracycline. Docetaxel plus capecitabine yielded significant improvements in overall response rate (ORR) (42% vs. 30%), TTP (6.1 vs. 4.2 months), and OS (14.5 vs. 11.5 months) compared with docetaxel alone.[9] Also the combination of paclitaxel and gemcitabine resulted in significant improvement in ORR (41.4% vs. 26.2%), TTP (6.14 vs. 3.98 months), and median OS (18.6 vs. 15.8 months) compared with paclitaxel alone.[10]

The estimated 5-year survival for MBC is 27%; however MBC remains an incurable disease. The aim of treatment in MBC is to improve progression-free survival and OS rates while improving quality of life through palliation of symptoms.[11] Anthracycline and taxane, which are the most active cytotoxic drugs in treating breast cancer, have been associated with several disadvantages such as cardiac and leukemogenic toxicities.[12] Under these circumstances, the search for new agents in the treatment of MBC has been undertaken in recent years.

Several drug combinations have been put to trial. The gemcitabine/cisplatin combination was both effective and tolerable as first-line therapy in patients with MBC pretreated with anthracyclines. Results revealed an ORR of 57.9%, median survival of 22 months, and TTP of 12.5 months.[13] Another combination involved cisplatin and vinorelbine. The basis for the combination of these 2 agents was dependent primarily on their toxicity profile and documented activity and synergism. Vinorelbine/cisplatin was administered both to patients treated previously with anthracyclines and to those not treated previously. The regimen resulted in a response rate of 52.9%, median TTP of 8.5 months, and a median survival of 16.6 months. The results of the trial concluded that vinorelbine/cisplatin is active and tolerable in MBC in both untreated and pretreated patients.[14] In another study with patients with MBC who were pretreated with docetaxel and anthracyclines, vinorelbine/cisplatin was administered to patients whose disease progressed after their initial treatment. Results revealed an ORR of 47.2%, a median TTP of 16 weeks, and a median OS of 36 weeks.[15] When used as a salvage regimen in patients relapsing after being pretreated with chemotherapy, vinorelbine/cisplatin resulted in an ORR of 61%, with 50% survival at 1 year, 12% at 2 years, and 8% at 3 years.[16] In a previous study using vinorelbine/cisplatin as first-line therapy in MBC, we reported an ORR of 64% and a median survival of 19 months.[17] These results show that cisplatin and vinorelbine used as first- and second-line treatment are effective. However a cisplatin use has been associated with several side effects such as nausea, vomiting, ototoxicity, and grade 3/4 neurotoxicity and nephrotoxicity, which mandate the use of a nontoxic alternative agent.

Liposomal cisplatin (lipoplatin), which has a mechanism of action similar to that of cisplatin, has substantially reduced toxicities compared with cisplatin, with efficacy that is enhanced or similar to that of cisplatin.[18] Based on these considerations, we wanted to determine the ORR, time to treatment failure (TTF), and OS in the treatment of MBC using lipoplatin in combination with vinorelbine and to study the efficacy and toxicity of this regimen.

Patients and Methods

Patient Selection

Eligible patients had histologically or cytologically proven MBC with a bidimensionally measurable lesion regardless of previous adjuvant treatment. Patients had a World Health Organization (WHO) performance status of 0-2, adequate hepatic and renal function (creatinine clearance $>$ 60 mL/min), and adequate bone marrow reserve (white blood cell count $>$ 3000/mm^3, absolute neutrophil count [ANC] $>$ 1000/mm^3, and platelet count $>$ 100,000/mm^3). Patients were 18-75 years of age and had a life expectancy of more than 3 months. The institutional review boards of the participating centers approved the study. Signed informed consent forms were collected from all enrolled subjects.

Patients were excluded if they were pregnant or breast-feeding; had a history of previous malignancies (except for excised carcinoma in situ of the cervix or nonmelanoma skin cancer); had central nervous system metastasis; had grade III or IV neuropathy (National Cancer Institute [NCI] grading system); had renal insufficiency (creatinine clearance $<$ 60 mL/min); had bone metastasis as the sole site of metastasis; had evaluable but not measurable disease (pleural effusion, ascites, pericardial effusion); had radiation therapy to all areas of measurable disease $<$ 4 weeks before treatment; had received or are receiving treatment with experimental drugs; had hypersensitivity to cisplatin, vinorelbine, lipoplatin, or any of their components; or had HER-2/neu overexpression (3+ on immunohistochemical testing or positive on fluorescence in situ hybridization).

Assessment of Response and Toxicity

Pretreatment evaluation included a medical history and physical examination; vital signs and performance status assessment; liver function tests; chemistry profile; complete blood cell (CBC) count and platelet count; bone scan; computed tomography scan of chest, abdomen, and pelvis; histologic determination of breast cancer; and

hormonal and HER-2/neu status. Clinical monitoring, with CBC count and creatinine and electrolyte determinations, were performed weekly; and liver function tests were performed every 3 weeks. Toxicity was evaluated according to the NCI grading system.

Response rates were graded according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Complete response (CR) was defined as the disappearance of all target lesions. Partial response (PR) required at least a 30% decrease in the sum of the largest diameter (LD) of target lesions, taking as reference the baseline sum LD. Progressive disease (PD) required at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of the LD recorded since the treatment started or the appearance of 1 of more new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the LD since the treatment started.

To assess safety of treatment, the disease and patient status was assessed before each cycle of chemotherapy. The following were carried out to assess safety: performance status assessment; toxicity grading; physical examination and vital signs assessment; measurement of CBC, platelets, blood urea nitrogen, creatinine, electrolyte, and calcium and magnesium levels; and liver function tests.

Treatment was discontinued if there was PD, severe neurotoxicity, ototoxicity, or nephrotoxicity, or if the patient withdrew from the study.

Treatment Plan

Patients received lipoplatin 120 mg/m^2 (days 1, 8, and 15 in a 21-day cycle) in 1 L 5% dextrose intravenous drip over 6-8 hours and vinorelbine 30 mg/m^2 (days 1 and 8 in a 21-day cycle) in 100 mL normal saline solution intravenous drip over 6-8 minutes. Treatment was repeated every 21 days for a total of 6 cycles. It was recommended that no prechemotherapy or postchemotherapy hydration be instituted and that the patients be treated with adequate antiemetic therapy.

Chemotherapy would be given only if the ANC was $> 1000/mm^3$ and the platelet count was $> 100{,}000/mm^3$. Evaluation was carried out after the second, fourth, and sixth cycles. If there was any progression at any time during evaluation, the patient was offered an alternative therapy.

Statistical Analyses

All treated patients were included in the intent-to-treat (ITT) analysis and were analyzed for safety. The evaluable population was defined as all patients eligible for the trial who underwent a full evaluation of target and nontarget lesions and who had received at least 2 cycles of study treatment. The best available overall response was considered. Response rate was computed with the confidence interval (CI) at the 95% level. The Kaplan-Meier method was applied to TTF, time to disease progression, and OS. The analyses were performed using SPSS software version 18.0 (SPSS, Chicago, IL). Statistical significance was set at $P < .05$.

TTF was defined as the time from the start of the treatment until discontinuation of treatment for any reason (including progression of disease, treatment toxicity, and death). Time to disease progression was defined as the time from the start of treatment to disease progression. OS was defined as the time from the start of treatment to death or last follow-up. Response duration was defined as the time that the first response was documented to relapse (in responding patients).

Table 1 Patient Characteristics

Number of Patients	35	
Median Age, Years (Range)	52 (29-74)	
PS at Inclusion		
0	24	68.6%
1	10	28.6%
2	1	2.9%
Hormone Receptors		
ER^+ PR^+	24	68.6%
ER^- PR^-	6	17.1%
Others	5	14.3%
Metastatic Sites		
Liver	20	57.1%
Lymph Nodes	13	37.1%
Bone	17	48.6%
Lung	10	28.6%
Local Recurrence (Skin)	5	14.3%
Pleura	3	8.6%
Type of Metastatic Sites		
Visceral	26	74.3%
Nonvisceral	9	25.7%
Number of Metastatic Sites		
1	12	34.3%
2	16	45.7%
3 or More	7	20.0%
Previous Neoadjuvant Treatment		
Anthracyclines	15	42.9%
Taxanes	11	31.4%
Anthracyclines + Taxanes	6	17.1%
Hormone Therapy	17	48.6%

Abbreviations: ER = estrogen receptors; PR = progesterone receptors; PS = performance status.

Results

Patient Characteristics

Between August 2007 and July 2009, 35 patients with MBC were enrolled. Three patients were not evaluable for response but were included in the ITT analysis: 1 patient had early death, 2 patients were not assessable as a result of premature study discontinuation (they withdrew from the study after the first cycle, 1 patient because of grade 2 renal toxicity and the other patient because of grade 4 neutropenia and nausea/vomiting). Therefore 32 patients with measurable disease were assessable for disease response per protocol. The patient characteristics are described in Table 1. Patients typically had visceral metastases and good performance status. All had Her-2/neu–negative ($HER2/neu^-$) disease. Ninety percent of patients had re-

Table 2 Response to Treatment

Objective Response Rate (RECIST) Evaluable Population	N = 32	
Objective Response: CR + PR (95% CI)	17	53.1% (34.8-71.4)
CR	3	9.4%
PR	14	43.8%
SD	12	37.5%
Disease Control (CR + PR + SD)	29	90.6%
Progressive Disease	3	9.4%
Median Time to Response (Range)	58 days (35-144)	
Median Duration of Response (95% CI)	8 months (4.8-11.2)	

Abbreviations: CI = confidence interval; CR = complete response; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Figure 1 Time to Treatment Failure (TTF) in the Intent-To-Treat Population

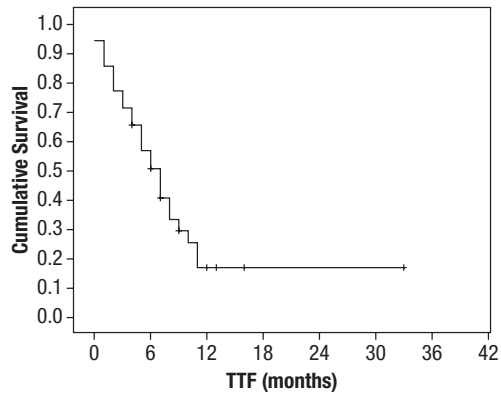


Figure 2 Time to Progression (TTP) in the Intent-To-Treat Population

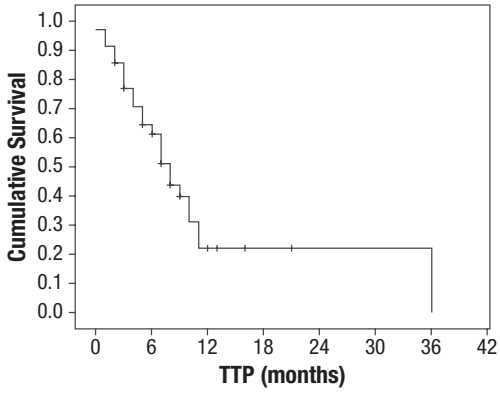
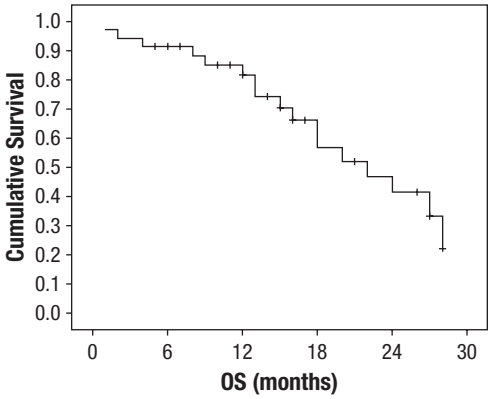


Figure 3 Overall Survival (OS) in the Intent-To-Treat Population



ceived earlier neoadjuvant chemotherapy, including anthracyclines and taxanes.

Clinical Efficacy

The total number of cycles administered was 174, with a median number of 6 cycles per patient (range, 1-9). The objective response rate was 53.1% among the 32 evaluable patients (95% CI, 34.8-71.4), including CRs in 9.4%. In the ITT population, the objective response rate was 48.6% (95% CI, 31.2-66.0). In the triple-negative subgroup of patients (n = 6), 1 patient achieved objective response. Median time to response was 58 days (range 35-144 days) and median duration of response was 8 months (95% CI, 4.8-11.2) (Table 2). Median TTF was 7 months (95% CI, 4.9-9.1) (Figure 1) and median TTP was 8 months (95% CI, 6-10) (Figure 2). After a median follow-up of 15.5 months, 18 of the 35 treated patients were still alive, and the median survival time was 22 months (95% CI, 14-30) (Figure 3).

Treatment-Related Toxicity

Table 3 shows the incidence of the most common grade 3/4 adverse events related to treatment. The most frequent hematologic toxicity was neutropenia, with grade 3/4 neutropenia being observed in 44% of cycles. Thirty percent of chemotherapy administrations were delayed because of grade 3/4 neutropenia. Only 4 patients (11.4%) experienced febrile neutropenia. Nonhematologic toxicities were mild. The main adverse event was nausea/vomiting, which was seen in 14.3% of patients. No WHO grade 3/4 nephrotoxicity or neuropathy was noted. Grade 1/2 renal toxicity was observed in 8 patients (22.9%). Renal toxicity was reversible within a median duration of 15 days (range 6-51). Asymptomatic hypomagnesemia was observed in 11 patients (31.4%). Three patients (8.6%) had to stop treatment because of toxicity (1 patient because of grade 2 renal toxicity, the second patient because of grade 4 neutropenia and nau-

Table 3 Treatment-Related Adverse Events Per Patient (%) – WHO Scale, N = 35

Event	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Nonhematologic				
Nausea/Vomiting	11 (31.4)	7 (20.0)	3 (8.6)	2 (5.7)
Neuropathy	3 (8.6)	1 (2.9)	0 (0.0)	0 (0.0)
Oral Stomatitis	2 (5.7)	1 (2.9)	0 (0.0)	0 (0.0)
Dyspnea	1 (2.9)	2 (5.7)	0 (0.0)	0 (0.0)
Diarrhea	3 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)
Renal	5 (14.3)	3 (8.6)	0 (0.0)	0 (0.0)
Symptomatic hearing loss	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	7 (20.0)	5 (14.3)	4 (11.4)	0 (0.0)
Anorexia	5 (14.3)	3 (8.6)	0 (0.0)	0 (0.0)
Hair Loss	6 (17.1)	2 (5.7)	0 (0.0)	0 (0.0)
Pain	8 (22.9)	3 (8.6)	1 (2.9)	0 (0.0)
Local Phlebitis	2 (5.7)	0 (0.0)	1 (2.9)	0 (0.0)
Hepatic	8 (22.9)	1 (2.9)	0 (0.0)	0 (0.0)
Hematologic				
Anemia	8 (22.9)	17 (48.6)	4 (11.4)	0 (0.0)
Neutropenia	1 (2.9)	4 (11.4)	10 (28.6)	15 (42.9)
Thrombocytopenia	3 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviation: WHO = World Health Organization.

sea/vomiting, and the third patient because of grade 3 asthenia, nausea/vomiting, and neutropenia).

Discussion

Liposomal cisplatin (lipoplatin) has a mechanism of action similar to that of cisplatin, resulting in apoptotic death of tumor cells; it inhibits DNA synthesis by the formation of DNA cross-links. Lipoplatin is composed of 8.9% cisplatin and 91.1% lipids.[19] Its liposomes are composed of dipalmitoylphosphatidylglycerol (DPPG), soy phosphatidylcholine, cholesterol and methoxypolyethylene glycol-distearoyl phosphatidylethanol amine. The anionic lipid DPPG gives lipoplatin its fusogenic properties, acting at the level of the entry of the drug through the cell membrane after reaching the target tissue. The polyethylene glycol coating gives the drug particles the ability to pass undetected by the macrophages and immune cells to remain in circulation after extravasation through the altered tumor vasculature. Lipoplatin accumulated in cancer tissue with altered vascularization 40 times more than in normal tissue, thereby reducing the potential toxic effects on normal tissue. Moreover, at the site of the cell membrane of tumor cells, where uptake is 4 times more than in normal cells, there was 160 times higher lipoplatin concentration in tumor cells compared with normal cells.[20] After measuring platinum levels in specimens from excised tumors and normal tissue, total platinum levels were 10-50 times higher in malignant tissue. Therefore lipoplatin damages more malignant tissue of both primary and metastatic origin.[20,21]

Lipoplatin has substantially reduced the renal toxicity, peripheral neuropathy, ototoxicity, and myelotoxicity, as well as the nausea/vomiting and asthenia of cisplatin in phase I, II, and III clinical trials.[18] In a very recent phase III trial, lipoplatin was much better tolerated than cisplatin in non-small cell lung cancer. The difference in toxicities was statistically significant in leukopenia, nausea/vomiting, and nephrotoxicity. In addition, asthenia was more common with cisplatin, with a statistically significant difference.[22]

The use of a vinorelbine/cisplatin regimen has been proven clinically effective and tolerable in the treatment of MBC. However cisplatin has been associated with several toxic effects, which directed the search for an effective alternative with a less toxic and more tolerable profile. Lipoplatin has been used in this trial as a substitute for cisplatin. The current prospective phase II trial was conducted to evaluate the use of vinorelbine plus lipoplatin in women with MBC in whom the majority had received previous adjuvant chemotherapy.

The results of our study show that the combination of vinorelbine/lipoplatin is effective in the treatment of MBC. Efficacy of the regimen is confirmed by a median TTP of 8 months (95% Cl, 4.8-11.2) and a median OS of 22 months (95% CI, 14-30). This regimen was also effective in achieving an ORR of 53.1%, with 9.4% of patients achieving a CR and 43.8% achieving a PR. These results are comparable to studies involving a vinorelbine/cisplatin regimen.

In the study by Mustacchi et al, the combination of vinorelbine/cisplatin achieved an ORR of 54.4% and a median OS of 21.2 months when used as first-line treatment in MBC.[14] Also, when used as first-line treatment, vinorelbine/cisplatin achieved an ORR of 64% and a median survival of 19 months.[17] When used as second-line treatment in 3 trials, the regimen achieved an ORR of 41%, 49%, and 25%, respectively.[15,23,24] The ORR reported in our study showed good results when compared with trials using vinorelbine/cisplatin as second-line treatment and better median survival when compared with trials using vinorelbine/cisplatin as first- and second-line treatment. These results show that vinorelbine/lipoplatin achieved comparable results in relation to ORR and better median survival when compared with vinorelbine/cisplatin.

Despite its effectiveness, the dose of cisplatin that can be administered is limited mainly by nausea, vomiting, and nephrotoxicity as well as other toxicities such as neurotoxicity and ototoxicity.[25,26] Studies involving vinorelbine/cisplatin reported grade 3/4 nausea and vomiting in 9%, 11%, 14%, and 17.3% of patients, respectively.[14,15,23,27] We report grade 3/4 nausea and vomiting in 14.3% of patients noting that grade 3/4 nausea and vomiting was the most common nonhematologic toxicity encountered in our study. Regarding grade 1/2 nephrotoxicity, it occurred in 22.9% of patients but was reversible within a median duration of 15 days. This percentage is higher than that reported in studies involving vinorelbine/cisplatin regimen. Neurotoxicity was markedly decreased in our study, with 11.5% of patients having grade 1/2 neurotoxicity. Results reported in studies involving cisplatin/vinorelbine showed 13.4%, 13.8%, 15%, and 24% grade 1/2 neurotoxicity, respectively.[14,15,23,27] Grade 3 neurotoxicity was seen in 5% of patients taking vinorelbine/cisplatin[23]; no grade 3/4 toxicities were observed in our study. Therefore nonhematologic toxicities were mild, with nausea and vomiting being the main adverse event, with results similar to ones achieved in trials involving vinorelbine/cisplatin. As for

grade 1/2 nephrotoxicity, the results were higher in our trial; however all cases were reversible. Concerning neurotoxicity, we reported results lower than studies involving vinorelbine/cisplatin.

As for hematologic toxicities, neutropenia was encountered most frequently in our trial, with grade 3/4 occurring in 71.5% of cases. Grade 3/4 neutropenia was lower than in the study reported by Ray-Coquard et al and higher than in 5 other trials.[14-17,27] Grade 3/4 neutropenia in our trial is probably attributed to previous administration of several cytotoxic agents in the majority of patients, which had reduced their bone marrow reserves. In addition, the weekly treatment schedule and the relatively high dose of vinorelbine (30 mg/m^2) might have contributed to the observed neutropenia.

In conclusion, the results of this trial reveal that vinorelbine/lipoplatin is effective in the treatment of patients with MBC and has achieved encouraging results regarding OS, TTP, and median survival. Also, the regimen is well tolerated with mild grade 1/2 and no grade 3/4 nephrotoxicity or neuropathy. However because the majority of patients in this trial received previous chemotherapy regimens, this warrants the investigation of this regimen as de novo first-line treatment in patients with MBC.

Clinical Practice Points

- Liposomal cisplatin (lipoplatin) has a mechanism of action similar to that of cisplatin with reduced toxicities and enhanced or similar efficacy.
- Thirty-five patients were included to assess the efficacy and safety of a lipoplatin-vinorelbine combination in a phase II clinical trial in metastatic breast cancer (MBC).
- The objective response rate was 53.1%. Complete remission was achieved in 3 patients (9.4%), partial response (PR) in 14 patients (43.8%), stable disease (SD) in 12 patients (37.5%), and progressive disease (PD) in 3 patients (9.4%). Median time to disease progression was 8 months (range 6-10 months).
- After a median follow-up of 15.5 months, 18 patients were still alive; the median survival time was 22 months (95% CI, 14-30).
- Neutropenia was the most frequent hematologic toxicity, with grade 3/4 neutropenia observed in 44% of cycles. Febrile neutropenia was observed in 4 patients (11.4%). No grade 3/4 nephrotoxicity or neuropathy was noted. Grade 1/2 nephrotoxicity occurred in 8 patients (22.9%) and grade 3 vomiting in 3 patients (8.6%).
- The results of this trial reveal that vinorelbine/lipoplatin is effective in treating patients with MBC and has achieved encouraging results regarding overall survival, time to disease progression, and median survival. The regimen is well tolerated with mild grade 1/2 and no grade 3/4 nephrotoxicity or neuropathy.
- Because the majority of patients in this trial received previous chemotherapy, this warrants the investigation of this regimen as de novo first-line treatment in patients with MBC.

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Disclosure

All authors report no relevant relationships to disclose.

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