Phase I/II study of biweekly vinorelbine and oxaliplatin as first-line treatment in patients with metastatic breast cancer

Antonio Guerrero[a], Sonia Servitja[b], Alvaro Rodríguez-Lescure[c], Lourdes Calvo[d], Sonia del Barco[e], María Teresa Quintanar[c], José Ignacio Juárez[f], Javier Gayo[f], Antonio Llombart[a] and Ignasi Tusquets[b]

The objective of this phase I/II study was to establish the recommended dose of biweekly vinorelbine and oxaliplatin in patients with metastatic breast cancer and to evaluate the efficacy and safety profile of this schedule as first-line treatment. Four different dose levels of vinorelbine and oxaliplatin were selected for the phase I study: (i) 25 and 80 mg/m^2; (ii) 25 and 90 mg/m^2; (iii) 25 and 100 mg/m^2; and (iv) 30 and 90 mg/m^2; respectively. At least three patients were treated at each dose level. Overall, 12 patients were included in the phase I trial. No dose-limiting toxicities occurred at any dose level. Therefore, the fourth dose level (30 mg/m^2 of vinorelbine and 90 mg/m^2 of oxaliplatin) every 2 weeks was selected for the phase II trial. In this part, 44 patients were included and 61% completed the eight 2-week cycles of study treatment. On an intention-to-treat basis, overall response rate was 59%, and median progression-free survival and overall survival were 9.2 months (95% confidence interval: 7.6–10.9) and 18.6 months (95% confidence interval: 14.4–22.9), respectively. The main severe toxicities were neutropenia (46%) and fatigue (14%). We conclude that the biweekly combination of vinorelbine and oxaliplatin at doses of 30 mg/m^2 and 90 mg/m^2, respectively, is highly active and well tolerated as first-line treatment for patients with metastatic breast cancer. *Anti-Cancer Drugs* 22:283–289 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2011, **22**:283–289

Keywords: anticancer drug combinations, biweekly drug administration schedule, cancer chemotherapy protocols, clinical trial, metastatic breast cancer, phase I, phase II

[a]Instituto Valenciano de Oncologia, Medical Oncology Service, Valencia, [b]Hospital del Mar, Medical Oncology Service, [c]Hospital General Universitario de Elche, Medical Oncology Service, Elche, [d]Complejo Hospitalario Universitario Juan Canalejo, Medical Oncology Service, A Coruña, [e]ICO-Hospital Josep Trueta, Medical Oncology Service, Girona and [f]Pierre Fabre Iberica, Division de Oncologia, Barcelona, Spain

Correspondence to Dr Ignasi Tusquets, MD, Medical Oncology Service, Hospital del Mar, Passeig Marítim 25-29, Barcelona 08003, Spain
Tel: +34 93 248 36 14; fax: +34 93 248 33 66;
e-mail: itusquets@parcdesalutmar.cat

Received 15 September 2010 **Revised form accepted** 7 November 2010

Introduction

Despite significant improvements in the treatment of metastatic breast cancer (MBC) [1,2], survival rates continue to be low. According to the Surveillance, Epidemiology and End Results cancer statistics review, the 5-year relative survival rate for MBC in the United States is only 23% compared with a rate of 98% for localized breast cancer [3]. Depending on the prognostic factors, including site of recurrence, axillary lymph node status at diagnosis, and estrogen receptor status [4], the median survival time for women with MBC may vary from 18 to 24 months [5].

Treatment of MBC is a major therapeutic challenge. Much of the difficulty lies in the fact that there are no clear guidelines on the optimal approach to treating these patients, and that several of the agents approved as first- or second-line therapy, such as trastuzumab and endocrine therapies, only benefit a limited number of patients [6]. In addition, patients have a significantly greater likelihood of experiencing adverse events (AEs) because of earlier exposure to chemotherapy [7]. Lastly, and very importantly, many women with breast cancer will probably have developed multiple drug resistance by the time they are diagnosed with advanced disease [8,9], greatly limiting the number of drugs that can be effectively administered. Approaches for overcoming these obstacles include the use of established drugs in combination with other cytotoxic agents, or endocrine and biological agents when appropriate [8,10]. In MBC, good results for combination therapies have been documented in phase II and phase III trials, including capecitabine and gemcitabine, docetaxel [11] or bevacizumab [12], lapatinib and paclitaxel [13], and vinorelbine and gemcitabine [14].

Vinorelbine is a semisynthetic vinca alkaloid that acts by inhibiting microtubule polymerization. The antitumor activity of vinorelbine is thought to be primarily because of the inhibition of mitosis at the metaphase through its interaction with tubulin [15]. Vinorelbine has been extensively used as single agent or in combination in the treatment of patients with MBC, and has been shown to be a very active compound in this setting, yielding objective response rates (ORR) of 36–50% and overall survival (OS) rates of 15.0–18.0 months [14,16,17]. Since the earliest studies of vinorelbine as first-line therapy in MBC,

0959-4973 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e3283425c55

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

intravenous doses of 30 mg/m^2 at different schedules have shown a manageable toxicity profile [14,16,17]. The most frequent severe toxicities of vinorelbine as single agent are leucopenia and neutropenia, which occur in 32% and 53% of patients, respectively [15].

Oxaliplatin is a diaminocyclohexane-containing platinum that induces formation of inter-strand and intra-strand platinum–DNA cross links, which result in the inhibition of DNA replication and transcription, and cell-cycle nonspecific cytotoxicity [18]. Oxaliplatin has shown efficacy against many tumor cell lines, including cisplatin-resistant and carboplatin-resistant lines [19]. In addition, because it has a target mechanism of action and mechanisms of resistance different from other platinum compounds, oxaliplatin may show additive and/or synergistic activity with different cyctotoxic agents [19–21].

Oxaliplatin has been shown to be moderately active in anthracycline-pretreated MBC patients when used as a single agent [22], but it is also a potentially promising agent for combination therapy as it has been shown to sensitize tumor cells to several cytotoxic agents, including cisplatin, carboplatin, and doxorubicin [19]. Moreover, in combination with other cytotoxic drugs, such as fluorouracil with or without vinorelbine, oxaliplatin has shown a manageable safety profile, even at doses of 130 mg/m^2 every 3 weeks [23,24]. The most frequent severe toxicities of oxaliplatin as single agent are fatigue and neuropathy, which occur in 9 and 7% of patients, respectively [18].

The safety of the combination of vinorelbine with oxaliplatin has been confirmed in a preliminary dose escalation study of patients with solid tumors, including breast cancer, who had failed at least one earlier chemotherapy regimen. At the recommended dose [RD; vinorelbine (27 mg/m^2) and oxaliplatin (50 mg/m^2) on days 1 and 8 every 3 weeks] the main AEs observed were grade 3/4 neutropenia (18% of cycles), grade 2/3 nausea/vomiting (13% of cycles), grade 2 neurotoxicity (5% of cycles), and grade 2/3 asthenia (16% of cycles) [25].

On account of their differing mechanisms of action and the favorable safety profile of the combination, vinorelbine with oxaliplatin may represent an interesting alternative in the management of patients with MBC. However, different doses and treatment regimens, which could potentially yield better outcomes, have not yet been explored.

Taking into account all these factors, we conducted a phase I study to determine the maximum tolerated dose (MTD) and the RD of intravenous vinorelbine and oxaliplatin given every 2 weeks to patients with MBC. On the strength of the results from this study, we conducted a phase II study in which the RD of vinorelbine and oxaliplatin was administered to determine the efficacy and safety profile of this schedule as first-line treatment of MBC.

Patients and methods

Study design

This phase I/II multicenter, prospective, nonrandomized study was carried out at five Spanish centers. The protocol was approved by the Clinical Research Ethics Committee at each participating site and the Spanish Medicine Agency (AEMPS Registration No.: 03–0315). The study procedures were carried out in accordance with the Declaration of Helsinki of 1975, as revised in 2000, and Good Clinical Practice guidelines. Written informed consent was obtained from all patients before enrollment.

Eligibility

Eligible patients were aged 18 years or above, had histologically confirmed MBC, and at least a measurable metastasis according to the Response Evaluation Criteria in Solid Tumors (RECIST). All patients had to have adequate hematological, renal, and hepatic functions [hemoglobin: > 10 g/dl; absolute neutrophil count (ANC): $> 2.0 \times 10^9$/l; platelet count: 100.0×10^9/l; creatinine clearance: ≥ 50 ml/min; serum bilirubin level: < 2 mg/dl; aspartate aminotransferase and alanine aminotransferase levels $< 3 \times$ upper limit of normal], a Karnofsky performance status of 60% or above, and an estimated life expectancy of 3 months or above. Earlier adjuvant or neoadjuvant chemotherapy, and/or endocrine therapy were allowed, and also radiotherapy, provided that no more than 30% of the bone marrow reserve was affected.

Exclusion criteria included pregnant or lactating women; women of childbearing age not using medically accepted contraceptive methods; earlier chemotherapy for metastatic disease; central nervous system involvement; earlier grade of more than 1 peripheral neuropathy; patients with concomitant tumors, or a history of other malignancies in the last 5 years (except for basal cell carcinoma or in-situ cervical cancer); having been treated with an investigational drug during the 30 days before study enrollment; significant uncontrolled comorbidities (such as diabetes mellitus, arterial hypertension), or any other serious medical or psychiatric conditions that would threaten the patient's life or impair the ability to receive protocol treatment.

Study procedures

Phase I

During the phase I study, patients were treated with escalating doses of vinorelbine (25–30 mg/m^2 intravenously on day 1) and oxaliplatin (80–100 mg/m^2 intravenously on day 1) in 2-week cycles. Four different dose levels of vinorelbine and oxaliplatin were established: (i) 25 and 80 mg/m^2; (ii) 25 and 90 mg/m^2; (iii) 25 and 100 mg/m^2; and (iv) 30 and 90 mg/m^2, respectively.

MTD was determined on the basis of the occurrence of any dose-limiting toxicity (DLT) during the first two cycles of study treatment or during the 2 weeks after these cycles. DLTs were defined as (i) grade 4 neutropenia (ANC

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

$< 0.5 \times 10^9$/l) during greater than 5 days, (ii) grade 4 thrombocytopenia (platelet count $< 25.0 \times 10^9$/l) or thrombocytopenia of any grade associated with bleeding, (iii) febrile neutropenia (fever $> 38.5°$C associated with grade 3–4 neutropenia), (iv) sepsis associated with grade 3/4 neutropenia, (v) any grade 3/4 nonhematological toxicity or grade 3/4 toxicity in laboratory parameters of clinical significance during the first cycle, excluding alopecia or inadequately treated anemia.

At least three patients were treated at each dose level. If none of the three patients experienced a DLT, the next dose level was started. If a DLT occurred in one patient, three additional patients were treated at the same dose level. The MTD was defined as the dose level at which at least two out of three or three out of six patients experienced a DLT. The dose level immediately below the MTD was considered to be the RD, and thus selected for further development in the phase II trial.

Phase II

During the phase II study, patients were treated with the RD of vinorelbine and oxaliplatin selected during the phase I trial. Treatment was administered for a maximum of eight cycles unless there was evidence of unacceptable toxicity or disease progression.

Dose modifications were made if ANC of less than 1.5×10^9/l, platelet count of less than 100.0×10^9/l, and/or there was documented febrile neutropenia. In this case, treatment was interrupted for up to 2 weeks until resolution, and doses of vinorelbine and oxaliplatin were reduced permanently by 15% in subsequent cycles. If toxicity did not resolve after 2 weeks, the patient was withdrawn from the study. Doses of both agents were permanently reduced by 75% in patients who experienced any grade 3 nonhematological toxicity (except alopecia and inadequately treated nausea/vomiting). In addition, patients who experienced any grade 4 nonhematological toxicity were withdrawn from the study.

In addition, the dose of oxaliplatin was reduced by 25% in patients who experienced painful paresthesia and/or dysesthesia, or paresthesia associated with functional impairment for a period of 8–13 days. In patients who experienced persistent mild paresthesia, oxaliplatin was interrupted until resolution, and reinitiated at a reduced dose (25% dose reduction). Oxaliplatin was permanently interrupted in case of persistent painful paresthesia or paresthesia associated with functional impairment.

Study assessments

A comprehensive health assessment, including Karnofsky Performance Status, complete and differential blood counts, and biochemical analysis including serum creatinine, glucose, alkaline phosphatase, bilirubin, aspartate aminotransferase, alanine aminotransferase, total serum protein, albumin, and prothrombin, were carried out at baseline, on day 1 of each cycle, and at the end of the last treatment cycle.

In addition, measurement of carcinoembryonic antigen and CA 15-3, and imaging studies, including abdomino–pelvic computed tomography scan, bone scintigraphy, and/or thoracic radiography, were carried out for every four treatment cycles to evaluate tumor response during treatment. On the completion of treatment, the patients were followed every 3 months.

The evaluation of the clinical response was made after the first four treatment cycles and repeated after eight treatment cycles. In responding patients, confirmatory assessments were made 4 weeks after the initial determination of the response. The evaluation of measurable responses was made according to RECIST (*http://www3.cancer.gov/bip/RECIST.htm*).

AEs were graded according to the National Cancer Institute Common Toxicity Criteria(version 2.0, updated on 18 August 1999), except for neurological toxicity, which was graded according to a scale developed specifically for oxaliplatin [26].

Statistical analysis

The primary endpoint of the phase I study was to determine the MTD of the biweekly combination of vinorelbine and oxaliplatin in patients with MBC and to establish the RD for further development in the phase II study.

The primary objective of the phase II study was to determine the ORR of the biweekly combination of vinorelbine and oxaliplatin administered at the RD established from the earlier phase I study as first-line treatment of patients with MBC. Secondary objectives included the assessment of progression-free survival (PFS), OS, and the evaluation of the safety profile of the new schedule.

Using a Simon two-stage minimax design, the targeted response rate was set at 50% ($P_1 = 0.5$), with a null rate of 30% ($P_0 = 0.3$), a type I error (α) of 0.1, a study power of 90% ($\beta = 0.1$), and the sample size was estimated at 39 assessable patients. Taking into account a dropout rate of 10%, the final sample size was increased to 43 patients.

Efficacy and safety analyses were carried out on an intention-to-treat population, comprising all patients who received at least one dose of study medication. PFS was defined as the time from trial registration until disease progression. Death was regarded as a progression event in patients who died before disease progression. OS was calculated as the time from trial registration until the date of death for any reason.

In both phase I and phase II studies, the categorical variables were described as percentages and absolute frequencies, and continuous variables were described using mean, median, minimum and maximum values, and 95%

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

confidence intervals (CI). In addition , in the phase II study, median PFS and OS were estimated by the Kaplan–Meier method.

Results

Phase I

From January to October 2004, a total of 12 patients were enrolled. The median age was 58 years (range: 39–78 years). Most patients (83%) had received earlier (neo) adjuvant chemotherapy.

A total of seventy-one 2-week cycles were administered. The median number of cycles per patient was six (range: 2–12 cycles). Six patients (50%) required dose reductions: all of them because of hematological toxicity; and nine patients (75%) required treatment delays. During treatment administration, the doses of both drugs were reduced in 11 cycles (15%) because of hematological toxicity (10 cycles) and one according to the investigator's criterion. In addition, 19 (27%) were delayed because of hematological toxicity (18 cycles) and one because of nonhematological toxicity.

According to the protocol's definition, no DLTs occurred in any of the four dose levels during the first two cycles. Grade 3 neutropenia occurred in two patients (17%) and grade 3 neurotoxicity and grade 3 pain occurred in one patient each (8%). No other severe AEs occurred during this period. Severe toxicities in the following cycles are reported in Table 1.

On the basis of these results, the RD was established at dose level 4 (biweekly doses of 30mg/m^2 and 90 mg/m^2) for vinorelbine and oxaliplatin, respectively, for further development in the phase II trial.

Phase II

Baseline patient characteristics

Between November 2004 and January 2008, 44 patients from five participating centers were enrolled. Median age was 59 years (range: 33–83 years) and 34 patients (77%) had received earlier (neo)adjuvant chemotherapy, consisting of anthracyclines in 50% or anthracyclines plus taxanes in 32%. Overall, 11 patients (25%) had triple-negative breast tumors. Twenty patients (46%) had one site of metastatic involvement, and eight (18%) had three or more. Detailed patient characteristics are listed in Table 2.

Twenty-seven patients (61%) completed the eight 2-week cycles established in the protocol. The reasons for the early discontinuation for the other 17 patients were disease progression ($n = 11$), investigator's criterion ($n = 4$), and unacceptable AEs ($n = 2$), which consisted of grade 4 dysarthria and decreased overall strength in one patient, and grade 4 neutropenia in another patient.

Treatment administration

A total of 290 chemotherapy cycles were administered during the phase II trial. Patients received a median of eight 2-week cycles (range: 1–8). Thirty-one patients (70%) received six or more chemotherapy cycles, with 27 (61%) patients having received the eight cycles planned. During the administration of the treatment, 85 cycles (29%) had to be delayed, and in 37 cycles (13%) the doses of vinorelbine and oxaliplatin were reduced. Hematological toxicity was the most common reason for both dose delays and reductions. The median absolute and relative dose intensities of vinorelbine and oxaliplatin were 12 mg/m^2 (82%) and 36 mg/m^2 (79%), respectively.

Table 1 Incidence of severe adverse events during the phase I trial (*N*=12)

	First two cycles		Following cycles	
Severe AEs	No. of patients [*n* (%)]	Grade	No. of patients [*n* (%)]	Grade
Dose level 1 (*N*=3)				
Neutropenia	1 (33)	3	1 (33)	4
Neurotoxicity	–	–	1 (33)	3
Dose level 2 (*N*=3)				
Neutropenia	–	–	1 (33)	3
Dose level 3 (*N*=3)				
Neutropenia	–	–	1 (33)	3
GGT elevation	–	–	1 (33)	3
Dose level 4 (*N*=3)				
Neutropenia	1 (33)	3	1 (33)	3
Neurotoxicity	1 (33)	3	–	–
Pain	1 (33)	3	–	–
Fatigue	–	–	1 (33)	3

AEs, adverse events; GGT, γ-glutamyl transferase.

Table 2 Baseline patient characteristics of the phase II trial

Characteristic	No. of patients [*n* (%)]
Age, median (range) (*N*=44)	59 (33–83)
<65 years	27 (61)
≥ 65 years	17 (39)
Karnofsky performance status (*N*=41)	
80%	3 (7)
90%	13 (32)
100%	25 (61)
Hormone receptor status	
ER+ (*N*=41)	28 (68)
PR+ (*N*=40)	20 (50)
Earlier neoadjuvant or adjuvant CT (*N*=44)	34 (77)
Type of previous CT (*N*=34)	
Anthracyclines	17 (50)
Anthracyclines plus taxanes	11 (32)
CMF	5 (15)
Unknown	1 (3)
Earlier endocrine therapy (*N*=44)	25 (57)
Earlier radiotherapy (*N*=44)	29 (66)
Number of metastatic sites (*N*=44)	
1	20 (46)
2	16 (36)
≥ 3	8 (18)
Metastatic sites[a] (*N*=44)	
Bone	22 (50)
Lung	19 (43)
Liver	15 (36
Local recurrence	12 (27)
Soft tissues	5 (11)
Other	6 (14)

CMF, cyclophosphamide, methotrexate and 5-fluorouracil; CT, chemotherapy; ER+, estrogen receptor positive; PR+, progesterone receptor positive.
[a]One patient may have had more than one metastatic site.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Efficacy

In the intention-to-treat population, complete response was observed in four patients (9%) and partial response in 22 patients (50%), with an ORR of 59% (95% CI: 43–74). In addition, seven patients (16%) had stable disease, and nine patients (20%) had progressive disease (Table 3).

After a median follow-up period of 16.8 months (range: 2.7–54.2), a median PFS of 9.2 months (95% CI: 7.6–10.9) and a median OS of 18.6 months (95% CI: 14.4–22.9) were observed (Figs 1 and 2). PFS and OS at 12 months were 45% (95% CI: 29–61) and 75% (95% CI: 61–89), respectively.

Specifically, in the 11 patients who had earlier received anthracyclines and taxanes in the neoadjuvant or the adjuvant setting, one patient achieved a complete response and five patients obtained partial responses with an ORR of 55% (95% CI: 23–83). Median OS and PFS were 13.3 months (95% CI: 9.2–17.4) and 6.4 months (95% CI: 1.4–11.3), respectively, in this subgroup of patients.

There were no statistically significant differences observed in efficacy in patients with triple-negative tumors versus non-triple-negative tumors with regard to median PFS ($P = 0.748$) and OS ($P = 0.840$).

Safety

Severe treatment-related AEs per patient and per cycle are summarized in Table 4. Grade 3/4 hematological AEs were neutropenia in 20 patients (46%) and 39 cycles (13%); anemia in two patients (5%) and three cycles (1%); and leucopenia in two patients (5%) and two cycles (1%). The most common grade 3/4 nonhematological toxicity was asthenia (six patients, 14%). Grade 3/4 neurotoxicity and constipation were observed in three patients (7%) and in one patient (2%), respectively.

Discussion

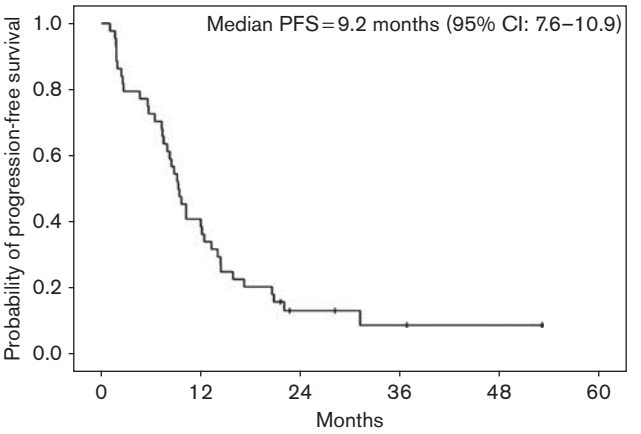
We conducted a phase I/II study to evaluate the efficacy and safety of the RD of vinorelbine and oxaliplatin as first-line treatment of patients with MBC. During the phase I study, the patients were treated with escalating doses of vinorelbine (25–30 mg/m^2 intravenously on day 1) and oxaliplatin (80–100 mg/m^2 intravenously on day 1) every 2 weeks. According to the protocol's definition, no DLTs occurred in any of the four dose levels during the first two cycles. Therefore, the last dose level at which

Table 3 Efficacy results on intent-to-treat population of the phase II trial (*N*=44)

	ITT population
Outcome	*n* (%)
Complete response	4 (9)
Partial response	22 (50)
Stable disease	7 (16)
Progressive disease	9 (20)
Not evaluable	2 (5)
ORR (percentage) (95% CI)	59 (43–74)
Median OS (months) (95% CI)	18.6 (14.4–22.9)
Median PFS (months) (95% CI)	9.2 (7.6–10.9)

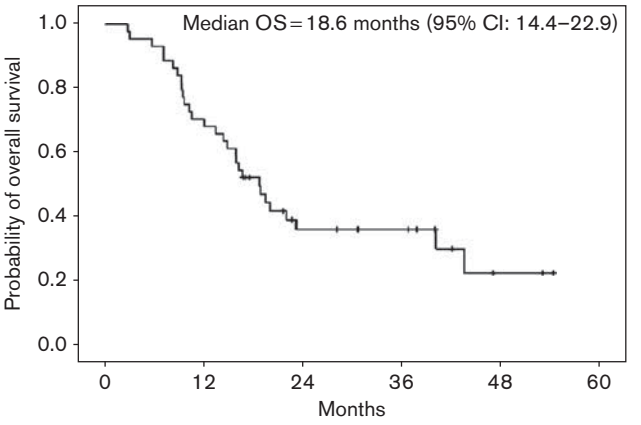
CI, confidence interval; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Fig. 1



Median progression-free survival (PFS, *N*=44). CI, confidence interval.

Fig. 2



Median overall survival (OS, *N*=44). CI, confidence interval.

Table 4 Incidence of severe adverse events per patient and per cycle during the phase II trial (*N*=44)

	Per patient (*n*=44) *n* (%)		Per cycle (*n*=290) *n* (%)	
Toxicity	Grade 3	Grade 4	Grade 3	Grade 4
Hematological				
Anemia	2 (5)	0 (0)	3 (1)	0 (0)
Leucopenia	2 (5)	0 (0)	2 (1)	0 (0)
Neutropenia	14 (32)	6 (14)	30 (10)	9 (3)
Nonhematological				
Asthenia	6 (14)	0 (0)	9 (3)	0 (0)
Constipation	1 (2)	0 (0)	2 (1)	0 (0)
Fatigue	6 (14)	0 (0)	9 (3)	0 (0)
Neurotoxicity	3 (7)	0 (0)	3 (1)	0 (0)

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

vinorelbine and oxaliplatin were administered at doses of 30 mg/m^2 and 90 mg/m^2, respectively, was selected for further development of the phase II study.

Subsequently, the results obtained during the phase II study showed that the biweekly administration of vinorelbine and oxaliplatin at the selected RD was an active and safe regimen as the first-line treatment in MBC. With an ORR of 59% (including 9% of patients with CR), an estimated PFS of 9.2 months, and an OS of 18.6 months, these results seem encouraging in view of the disease under study. Interestingly, efficacy remained in patients with triple-negative tumors and in patients pretreated with anthracyclines and taxanes.

In an earlier phase II trial by Petit *et al.* [27], vinorelbine (26 mg/m^2) and oxaliplatin (130 mg/m^2) given every 3 weeks to 42 patients with MBC produced an ORR of 27% (95% CI: 14–43), and a median time to progression and OS of 3.4 months (95% CI: 2.0–4.8) and 12.7 months (95% CI: 7.7–17.6), respectively. There are several reasons inherent to the designs of the studies by both Petit *et al.* and us which may explain the differences in efficacy observed. In the study by Petit *et al.* the patients received an equivalent of 8.7 mg/m^2/week of vinorelbine and 43.3 mg/m^2/week of oxaliplatin, whereas in our study, the dose of vinorelbine was almost double (15 mg/m^2/week). In addition, in the study carried out by Petit *et al.*, the patients received a median of four cycles, whereas in our study a median of eight cycles were administered. Furthermore, with regard to patient characteristics, in their study all patients had to have received at least one taxane-based and one anthracycline-based regimen, either as adjuvant therapy or for metastatic disease [27], whereas in our study patients were not treated for advanced disease and only 32% of them had earlier received both anthracyclines and taxanes.

Tumor resistance is a major problem encountered in the setting of MBC. To date, the most widely studied cellular mechanisms of tumor resistance are those associated with the mechanisms involving efflux transporters, such as P-glycoprotein, MDR1, and MRP1 [28]. Anthracyclines, taxanes, vinca alkaloids, and platinum compounds are substrates of these proteins in varying degrees, and therefore could be affecting the patient's response to vinorelbine and/or oxaliplatin therapy [9]. In fact, earlier exposure to cytotoxic drugs or endocrine therapy is shown to be associated with an increased proportion of tumors expressing MDR1/P-glycoprotein, and there is evidence indicating that patients with tumors expressing these proteins are three times more likely to fail to respond to chemotherapy than patients whose tumors are MDR1/P-glycoprotein negative [29].

If the efficacy results obtained with this combination are compared with either drug administered as monotherapy, it seems that the combination of both drugs may improve the outcome of these patients. Thus, Garufi *et al.* [22] administered 130 mg/m^2 of oxaliplatin every 3 weeks to patients with MBC and observed an ORR of 21% and a median OS of 12.0 months. In an earlier trial by the Grupo Español de Investigación del Cáncer de Mama trial, 30 mg/m^2 of vinorelbine was administered on days 1 and 8 every 3 weeks to patients with locally recurrent or MBC who were pretreated with anthracyclines and taxanes [14]. An ORR of 26% with a median PFS and OS of 4.0 months and 15.9 months, respectively, was observed.

With regard to the safety profile, we consider that the study treatment administered during the phase II study was manageable and well tolerated, with 61% of patients having completed the eight 2-week cycles. During treatment administration, the main severe hematological toxicity was neutropenia, which occurred in 47% of patients (14% of them with grade 4). Other severe toxicities observed were asthenia (14% of patients), and neurotoxicity (7%). Although neurotoxicity is the main toxicity of oxaliplatin, which can be worsened by the addition of vinorelbine, in our study grade 4 neurotoxicity was not observed and only three patients experienced grade 3 neurotoxicity. In the study by Petit *et al.* [27], 79% of patients developed severe neutropenia and 17% of patients showed severe thrombocytopenia, whereas grade 3 neurotoxicity was observed in 21% of patients. Despite the fact that we administered a combination of vinorelbine and oxaliplatin every 2 weeks rather than every 3 weeks, and consequently, a greater systemic accumulation of drugs and a greater toxicity may have been expected, this was not apparently the case.

In conclusion, the biweekly combination of vinorelbine (30 mg/m^2) and oxaliplatin (90 mg/m^2) warrants further exploration because of its manageable safety profile and high clinical efficacy as first-line treatment in patients with MBC. Differences in the mechanisms of action between vinorelbine and oxaliplatin, and the fact that neither of them have cross-resistance to taxanes or anthracyclines, add to the benefits of this combination.

Acknowledgements

The authors thank Francisco Javier Pérez Martin (Barcelona, Spain) for carrying out the statistical analysis of the study, Dr Ximena Alvira from HealthCo (Madrid, Spain) for providing medical writing services, José Ignacio Juárez for monitoring and data management, and Pierre Fabre Ibérica for the financial funding of the project.

The authors declare that they do not have any conflict of interest that may inappropriately influence this work.

Part of this study was presented as a poster at the 42nd Annual Meeting of the American Society of Clinical Oncology (ASCO), Atlanta, Georgia, USA, 2006, at the 44th Annual Meeting of the ASCO, Chicago, IL, USA, 2008, and at the 14th European Cancer Conference (ECCO), Barcelona, Spain, 2007.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

References

1 Gennari A, Conte P, Rosso R, Orlandini C, Bruzzi P. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 2005; **104**:1742–1750.

2 Chia SK, Speers CH, D'Yachkova Y, Kang A, Malfair-Taylor S, Barnett J, *et al.* The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 2007; **110**:973–979.

3 National Cancer Institute (NCI). Surveillance Epidemiology and End Results (SEER) cancer statistics review 1999–2005. *http://www.seer.cancer.gov/csr/1975_2006/browse_csr.php?section=4&page=sect_04_table.12.html#table3*. [Accessed on 8 February 2010]

4 Insa A, Lluch A, Prosper F, Marugan I, Martinez-Agullo A, Garcia-Conde J. Prognostic factors predicting survival from first recurrence in patients with metastatic breast cancer: analysis of 439 patients. *Breast Cancer Res Treat* 1999; **56**:67–78.

5 O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist* 2005; **10** (**Suppl 3**):20–29.

6 Gligorov J, Lotz JP. Optimal treatment strategies in postmenopausal women with hormone-receptor-positive and HER2-negative metastatic breast cancer. *Breast Cancer Res Treat* 2008; **112** (**Suppl 1**):53–66.

7 Carrick S, Parker S, Thornton CE, Ghersi D, Simes J, Wilcken N. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* 2009; **15**:CD003372.

8 Dean-Colomb W, Esteva FJ. Emerging agents in the treatment of anthracycline- and taxane-refractory metastatic breast cancer. *Semin Oncol* 2008; **35** (**2 Suppl 2**):S31–S38. quiz S40.

9 Coley HM. Mechanisms and strategies to overcome chemotherapy resistance in metastatic breast cancer. *Cancer Treat Rev* 2008; **34**:378–390.

10 Moreno-Aspitia A, Perez EA. Anthracycline- and/or taxane-resistant breast cancer: results of a literature review to determine the clinical challenges and current treatment trends. *Clin Ther* 2009; **31**:1619–1640.

11 Chan S, Romieu G, Huober J, Delozier T, Tubiana-Hulin M, Schneeweiss A, *et al.* Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. *J Clin Oncol* 2009; **27**:1753–1760.

12 Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, *et al.* Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 2005; **23**:792–799.

13 Di Leo A, Gomez HL, Aziz Z, Zvirbule Z, Bines J, Arbushites MC, *et al.* Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol* 2008; **26**:5544–5552.

14 Martín M, Ruíz A, Muñóz M, Balil A, García-Mata J, Calvo L, *et al.* Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. *Lancet Oncol* 2007; **8**:219–225.

15 Vinorelbine (Navelbine) *http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20388S014lbl.pdf*. [Accessed February 2010]

16 Fumoleau P, Delgado FM, Delozier T, Monnier A, Gil Delgado MA, Kerbrat P, *et al.* Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 1993; **11**:1245–1252.

17 Garcia-Conde J, Lluch A, Martin M, Casado A, Gervasio H, De Oliveira C, *et al.* Phase II trial of weekly IV vinorelbine in first-line advanced breast cancer chemotherapy. *Ann Oncol* 1994; **5**:854–857.

18 Oxaliplatin *http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021492s011,021759s009lbl.pdf*. [Accessed February 2010]

19 Raymond E, Faivre S, Woynarowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol* 1998; **25** (**2 Suppl 5**):4–12.

20 Rixe O, Ortuzar W, Alvarez M, Parker R, Reed E, Paull K, *et al.* Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. *Biochem Pharmacol* 1996; **52**:1855–1865.

21 Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. *Ann Oncol* 1998; **9**:1053–1071.

22 Garufi C, Nistico C, Brienza S, Vaccaro A, D'Ottavio A, Zappala AR, *et al.* Single-agent oxaliplatin in pretreated advanced breast cancer patients: a phase II study. *Ann Oncol* 2001; **12**:179–182.

23 Zelek L, Cottu P, Tubiana-Hulin M, Vannetzel JM, Chollet P, Misset JL, *et al.* Phase II study of oxaliplatin and fluorouracil in taxane- and anthracycline-pretreated breast cancer patients. *J Clin Oncol* 2002; **20**:2551–2558.

24 Delozier T, Guastalla JP, Yovine A, Levy C, Chollet P, Mousseau M, *et al.* A phase II study of an oxaliplatin/vinorelbine/5-fluorouracil combination in patients with anthracycline-pretreated and taxane-pretreated metastatic breast cancer. *Anticancer Drugs* 2006; **17**:1067–1073.

25 Kakolyris S, Kouroussis C, Koukourakis M, Mavroudis D, Malas K, Vardakis N, *et al.* A dose-escalation study of oxaliplatin and vinorelbine in patients with advanced solid tumors. *Oncology* 2002; **63**:213–218.

26 Caussanel JP, Lévi F, Brienza S, Misset JL, Itzhaki M, Adam R, *et al.* Phase I trial of 5-day continuous venous infusion of oxaliplatin at circadian rhythm-modulated rate compared with constant rate. *J Natl Cancer Inst* 1990; **82**:1046–1050.

27 Petit T, Benider A, Yovine A, Bougnoux P, Spaeth D, Maindrault-Goebel F, *et al.* Phase II study of an oxaliplatin/vinorelbine combination in patients with anthracycline- and taxane-pre-treated metastatic breast cancer. *Anticancer Drugs* 2006; **17**:337–343.

28 Gottesman MM. Mechanisms of cancer drug resistance. *Annu Rev Med* 2002; **53**:615–627.

29 Trock BJ, Leonessa F, Clarke R. Multidrug resistance in breast cancer: a meta-analysis of MDR1/gp170 expression and its possible functional significance. *J Natl Cancer Inst* 1997; **89**:917–931.

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.