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Research Paper

Phase I and II Study of Gemcitabine and Vinorelbine in Heavily Pretreated Patients with Metastatic Breast Cancer and Review of the Literature

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Abstract

Background: Many phase II trials investigated the combination of Gemcitabine (G) and Vinorelbine (V) in the treatment of metastatic breast cancer (MBC) with variable outcomes. This study was conducted to explore whether this combination was effective and tolerable in MBC patients who were heavily pretreated with anthracyclines and taxanes. *Methods*: A phase I study was conducted first to establish the maximum tolerated dose (MTD) of the G and V combination in MBC patients. Then, a phase II study evaluated the response rates, the median time to progression (TTP), the overall survival (OS) as well as the toxicities resulting from this combination at the MTD. *Results:* Nine patients were enrolled in the phase I study. The MTD was identified as 700mg/m^2 of G on days 1 and 8 in combination with 15 mg/m^2 of V on days 2 and 9, every 21 days. Twenty-one of 25 patients involved in the phase II study were evaluable for response. No complete or partial responses were achieved; 6 patients (24.0%) had stable disease and 15 (60.0%) progressed. The median TTP was 2 months and the median OS 10 months. Grade 3/4 Neutropenia was the major hematologic toxicity, occurring in 52% of the cycles. The most common non-hematologic grade 3/4 toxicities were fatigue (18%), myalgias (17%) and arthralgias (13%). *Conclusion*: In heavily pretreated patients with MBC, the combination of G and V at the doses stated above was ineffective as it did not induce partial or complete responses. Other chemotherapy agents or combinations should be evaluated in future studies.

Key words: Metastatic breast cancer, Gemcitabine, Vinorelbine, anthracycline, taxane.

Introduction

Anthracyclines and taxanes are the two most commonly used cytotoxic chemotherapy agents in the neoadjuvant and adjuvant treatment of breast cancer [1, 2]. However, recurrent tumors may have relative resistance to both classes of agents. Therefore, there is an increasing need for anthracycline- or taxane-free regimens to treat recurrent breast cancer after neoadjuvant and adjuvant chemotherapy.

Gemcitabine (2′, 2′-difluorodeoxycytidine) is a pyrimidine analog that is phosphorylated intracellularly to produce derivatives that inhibit DNA synthesis [3]. Many phase II studies have evaluated its use as

a single agent in the treatment of metastatic breast cancer (MBC), with overall response rates of 14% to 37% as first-line therapy and approximately 12% to 30% as second-line therapy after prior taxanes or anthracyclines [4]. The main side effects of the drug are granulocytopenia, thrombocytopenia, and abnormal liver function tests. However, gemcitabine is most effective when administered with a taxane (docetaxel or paclitaxel) in the first- or second-line setting [5]. Favorable responses and manageable toxicity profiles have also been reported when it is used in combination with other chemotherapeutic agents, such as anthracyclines and platinum compounds [6-10].

Vinorelbine is a semi-synthetic vinca alkaloid that induces cytotoxicity by inhibiting microtubule assembly at the G2-M phase. Most studies of vinorelbine as monotherapy, with or without granulocyte colony-stimulating factor, showed a mean overall response rate of 25% [11, 12]. Vinorelbine in combination with taxanes, anthracyclines, or platinum agents has shown efficacy in phase II and III trials in patients with anthracycline- or taxane-resistant recurrent breast cancer and MBC [13-21].

Gemcitabine and vinorelbine have different mechanisms of anti-tumor activity, good therapeutic indices, and no overlapping toxicities, except for neutropenia. In addition, both drugs appear to be non-cross-resistant with anthracyclines and taxanes. Such characteristics make the combination of gemcitabine and vinorelbine a promising treatment for MBC, especially in patients with previous exposure to taxanes or anthracyclines.

Multiple studies have been conducted in the past decade to evaluate the efficacy and tolerability of gemcitabine and vinorelbine in the treatment of advanced breast cancer or MBC. Response rates varied between studies and few of them included heavily pretreated patients. Here, we report the results of a phase I and II study of gemcitabine and vinorelbine in patients with MBC pretreated with anthracyclines and taxanes. The objectives of this study were to determine these drugs' maximum tolerated dose (MTD) and qualitative and quantitative toxicities, the toxicities' reversibility, and patients' response rate, time to progression (TTP), and survival duration.

Patients and Methods

Patient selection

All patients had histologically confirmed MBC and had been treated with two or more chemotherapy regimens in the metastatic setting. Consecutive eligible patients were recruited and treated at MD Anderson Cancer Center on an Investigational Review Board approved Phase I-II trial. Phase I patients were accrued between December 23, 1999 and December 1, 2000; phase II patients were accrued between December 29, 2000 and August 8, 2003. Pertinent information were retrieved from the electronic research data base that accessed and reviewed for the purpose of this report. Patients may have undergone hormonal therapy at any time. They were required to be ≥ 18 years, have a life expectancy of ≥ 12 weeks, have a Zubrod performance status of ≤ 2, and have adequate bone marrow, liver, and kidney function, defined as follows: absolute neutrophil count (ANC) ≥ 1,500/mcL, platelet count ≥ 100,000/mcL, total bilirubin level within the upper limits of the normal range, aspartate aminotransferase and alanine aminotransferase levels of ≤ four times the upper limit of the normal range, and serum creatinine level of ≤ 2.5 mg/dl. Patients were eligible if they had stable ≤ grade 1 peripheral neuropathy and if it had been ≥3weeks since radiation therapy or chemotherapy. All women of childbearing potential who did not use adequate contraception measures were excluded from the study, as were those with intercurrent medical conditions that were not well controlled by medication, concurrent active infections, neurotoxicity of ≥ grade 2, metastatic central nervous system disease diagnosed within the previous 6 months, or a history of another invasive malignancy. In addition, for the phase I study, patients were required to have measurable or evaluable disease by physical examination or radiological evaluation. MD Anderson institutional review board approval and patient informed consent were obtained in all cases.

Treatment plan

Phase I study design

Treatment was administered on an outpatient basis. Patients were treated with a starting dose of 700 mg/m²of gemcitabine by infusion, at a rate of 10mg/minute, on days 1 and 8. The starting dose of vinorelbine infusion, given on days 2 and 9, was 20mg/m² over 10 minutes. The cycle duration was 21 days. Dose levels are listed in **Table 1**, and dose modifications were adjusted by roughly 20% increments.

If no patients developed grade 3 or 4 non-hematologic toxicity or dose-limiting granulocytopenia or thrombocytopenia at any dose level, three patients would be treated at the next dose level. If one of three patients developed a grade 3 or 4 toxicity, or dose-limiting granulocytopenia or thrombocytopenia, three patients would be entered at the same dose level. If only two of six patients experienced a dose-limiting toxicity (DLT), three more patients would be added at the lower level. If two of three patients developed a DLT, the next patient

would be treated at a lower level. The MTD was one dose level below the dose at which three of six patients developed a grade 3 or 4 toxicity or dose-limiting granulocytopenia or thrombocytopenia. DLTs were febrile neutropenia (temperature > 38.1°C and ANC < 500/mcL), neutrophil count ≤1,000/mcL by day 29, and a platelet count < 20,000/mcL or one resulting in bleeding.

Table 1. Dose levels of gemcitabine and vinorelbine

Dose level	Gemcitabine (days 1 and 8) (mg/m²)	Vinorelbine (days 2 and 9) (mg/m²)
-3	500	15
-2	600	15
-1	700	15
0	700	20
1	850	20
2	1000	20
3	1000	25
4	1200	25
5	1200	30
6	1400	30
7	1400	37

Phase II study design

After the MTD had been determined, patients were treated at that dose level in the phase II study. All patients who underwent a minimum of two cycles of treatment were considered evaluable for response; however, if disease progressed rapidly, treatment was discontinued after one cycle and the condition was counted as progressive disease. TTP was defined as the period of time, on study, from the first day of treatment to when progressive disease was clearly documented. Survival duration was defined as the period of time from the first day of drug treatment to the date of death of the patient. All patients enrolled in the study were also evaluated for toxicity.

Patient evaluation

The pretreatment evaluation included a complete medical history and physical examination, with a performance status assessment. Hematological and full chemical work-ups were obtained, in addition to testing for tumor markers CA 27.29 and CEA. Imaging studies included chest x-ray, computed tomography, abdominal sonography, bone scan, plain films of areas of suspicious increased activity, and magnetic resonance imaging. The on-study evaluation included a complete physical examination during the week preceding therapy and every 3 weeks thereafter; a hematological survey on days 8, 12, 15, and 21 during the first two cycles and weekly for subsequent treatments; a chemistry profile, repeated every 6 weeks (SGPT, LDH, alkaline phosphatase, total bilirubin, BUN, creatinine, glucose, and calcium), and tumor markers CA 27.29 or CEA (every 6 weeks if initially elevated and every 12 weeks if not). All cancer-related symptoms and drug-associated adverse experiences were recorded every 3 weeks, per NCI Common Toxicity Criteria guidelines. Tumor measurements were obtained through physical examination or chest radiography every 6 weeks and through sonography, CT, MRI, bone scan, or bone radiography every 8 weeks when indicated. Patients were allowed to remain in the study in the absence of progressive disease or unacceptable toxicities, which were defined as unpredictable, irreversible, or grade 4 non-hematologic toxicities.

Results

Patient characteristics

Overall, 34 anthracycline- and taxane-pretreated MBC patients were enrolled in the study. As neoadjuvant or adjuvant, 8 patients had anthracycline and taxane; 10 patients had anthracycline with/out cyclophosphamide, methotrexate and flourauracil (CMF) and 4 patients had CMF only; 8 patients presented with no adjuvant or neoadjuvant chemotherapy. All patients were vinorelbine, gemcitabine or platinum compounds naïve. One patient received capecitabine in the adjuvant setting and 28 patients received it in the metastatic setting. Only 5 patients received trastuzumab: one in the adjuvant setting and 4 in the metastatic setting.

The phase I study involved nine patients, and phase II included 25. Patients' characteristics are shown in **Table 2.** All patients were women; most were white (74%), with a median age of 52 years and a performance status of 1 (62%). Fourteen patients (41%) had positive estrogen receptor status, and most (79%) had visceral disease. All patients had undergone chemotherapy with a median of three different regimens prior to enrollment; 21 (62%) had undergone chemotherapy in both the adjuvant and metastatic settings. Twenty-four (71%) patients had undergone radiation therapy as well, and 15(44%) had undergone hormonal therapy.

Phase I study

Dose escalation and DLT

Nine patients (three entered at level 0 and six at level -1) received a total of 54 cycles, with interpatient dose adjustment based on toxicities **(Table 3)**. Six cycles were administered at dose level 0, with a median ANC nadir of 850/mcL and a median platelet count nadir of 106,000/mcL; 28 at dose level -1, with a median ANC nadir of 900/mcL and a median platelet count nadir of 92,000/mcL; 18 at dose level -2, with a

median ANC nadir of 1,240/mcL and a median platelet count nadir of 131,000/mcL; and two at dose level -3, with a median ANC nadir of 1,110/mcL and a median platelet count nadir of 112,000/mcL. In conclusion, 700 mg/m^2 of gemcitabine on days 1 and 8, in combination with 15mg/m^2 of vinorelbine on days 2 and 9, given in a cycle of 21 days, was considered a safe dose level for most patients.

Table 2. Patient characteristics. All patients were female, and all underwent both taxane and anthracycline therapy.

Patient characteristic	Phase I	Phase II	Total
Number of patients	9	25	34
Median age, years (range)	50 (31-69)	52 (38-70)	52 (31-70)
Ethnic group, n (%)			
Black	0 (0)	4 (16)	4 (12)
Hispanic	1 (11)	4 (16)	5 (15)
Non-Hispanic white	8 (89)	17 (68)	25 (74)
ECOG performance status, n (%)			
0	3 (33)	7 (28)	10 (29)
1	4 (44)	17 (68)	21 (62)
2	2 (22)	1 (4)	3 (9)
Estrogen receptor status, n (%)			
Positive	6 (67)	8 (32)	14 (41)
Negative	3 (33)	17 (68)	20 (59)
Prior hormonal therapy, n (%)			
Yes	6 (67)	9 (36)	15 (44)
No	3 (33)	16 (64)	19 (56)
Prior radiation therapy, n (%)			
Adjuvant	4 (44)	10 (40)	14 (41)
Metastatic	2 (22)	4 (16)	6 (18)
Adjuvant and metastatic	0 (0)	4 (160)	4 (12)
None	3 (33)	7 (28)	10 (29)
Number of prior chemotherapy regimens, n (%)			
2	2 (22)	2 (8)	4 (12)
3	3 (33)	16 (64)	19 (56)
4	3 (33)	5 (20)	8 (24)
5 or 6	1 (11)	2 (8)	3 (9)
Prior chemotherapy setting, n (%)			
Adjuvant	0 (0)	1 (4)	1 (3)
Metastatic	5 (56)	7 (28)	12 (35)
Adjuvant and metastatic	4 (44)	17 (68)	21 (62)
Number of disease sites, n (%)			
1	2 (22)	5 (20)	7 (21)
2	3 (33)	9 (36)	12 (35)
3	0 (0)	2 (8)	2 (6)
4	2 (22)	6 (24)	8 (24)
5 or 6	2 (22)	3 (12)	5 (15)
Dominant site of disease, n (%)			
Soft tissue	0 (0)	4 (16)	4 (12)
Bone	1 (11)	2 (8)	3 (9)
Visceral	8 (89)	19 (76)	27 (79)

Table 3. Number of cycles and hematologic nadirs, according to gemcitabine and vinorelbine dose levels, in phase I. Abbreviations: G, gemcitabine; V, vinorelbine; AGC, absolute granulocyte count.

Dose level (mg/m^2)	Number of cycles	AGC nadir (range) (1,000 u/mcL)	Platelets nadir (range) (1,000 u/mcL)
All cycles	54	1.01 (0.01-3.06)	102 (33-358)
0: G=700, V=20	6	0.85 (0.04-1.10)	106 (55-358)
-1: G=700, V=15	28	0.90 (0.01-2.32)	92 (43-278)
-2: G=600, V=15	18	1.24 (0.08-3.06)	131 (33-302)
-3: G=500, V=15	2	1.11 (1.01-1.20)	112 (84-139)

Table 4. Incidence of NCI Common Toxicity Criteria grades 2, 3, and 4 adverse effects in phase I study (per cycle)

Toxicity (n=54)	Grade, n (%)			
	2	3	4	Total
Non-hematologic				
Abdominal pain	2 (4)	0 (0)	0 (0)	2 (4)
Alopecia	35 (65)	NA	NA	35 (65)
Arthralgias	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	7 (13)	2 (4)	0 (0)	9 (17)
Diarrhea	4 (7)	0 (0)	0 (0)	4 (7)
Fatigue	19 (35)	8 (15)	0 (0)	27 (50)
Headache	5 (9)	0 (0)	0 (0)	5 (9)
Mucositis	6 (11)	0 (0)	0 (0)	6 (11)
Myalgias	20 (37)	7 (13)	0 (0)	27 (50)
Nausea	11 (20)	2 (4)	0 (0)	13 (24)
Neutropenic fever	0 (0)	1 (2)	0 (0)	1 (2)
Neutropenic infection	0 (0)	0 (0)	0 (0)	0 (0)
Non-neutropenic fever	5 (9)	0 (0)	0 (0)	5 (9)
Non-neutropenic infection	0 (0)	2 (4)	0 (0)	2 (4)
Paresthesias	10 (19)	0 (0)	0 (0)	10 (19)
Rash/pruritus	2 (4)	0 (0)	0 (0)	2 (4)
Vomiting	5 (9)	0 (0)	0 (0)	5 (9)
Hematologic				
Neutropenia	16 (30)	14 (26)	12 (22)	42 (78)
Thrombocytopenia	11 (20)	2 (4)	0 (0)	13 (24)
Anemia	8 (15)	2 (4)	1 (2)	11 (20)

Toxicity

Overall, the chemotherapy regimen was well tolerated (**Table 4)**. All administered cycles were evaluable for hematologic and non-hematologic toxicities. The most common grade 2 non-hematologic toxicities were alopecia (65% of courses), myalgias (37%), and fatigue (35%). Grade 3 fatigue and myalgias were reported in 15% and 13% of cycles, respectively. No grade 4 non-hematologic toxicities were observed. Grade 2 neutropenia, thrombocytopenia, and anemia were present in 30%, 20%, and 15% of cycles, respectively. Grade 3 neutropenia, thrombocytopenia, and anemia were present in 26%, 4%, and 4%. Grade 4 neutropenia and anemia occurred in 22% and 2%, respectively; no grade 4 thrombocytopenia was reported.

The MTD was identified as 700mg/m² of gemcitabine on days 1 and 8 and15 mg/m² of vinorelbine on days 2 and 9.

Phase II study

Response evaluation

One patient in the phase I study had non-evaluable disease at baseline and was not evaluable for response. No responses were observed among the eight evaluable patients. The median TTP was 5 months (range, 1-12 months), and the median overall survival duration was 12 months (range, 2-46 months). Among the 25 patients treated in phase II, 21 were evaluable for response. The others developed central nervous system disease at the beginning of cycle 1 (one patient) or an intractable headache (one patient), were transferred to private oncologist care per patient request (one patient), or died of an unclear cause (one patient). With a median number of two cycles per patient, no complete or partial remissions were experienced **(Table 5)**; only six patients (24%) had stable disease, and 15(60%) experienced progression during therapy. The median TTP was 2 months (range, 1-6 months) and the median overall survival duration was 10 months (range, 1-36 months).

Overall, of the 34 patients who entered the study (phases I and II), 29 were evaluable for response. With a median number of 2.5 cycles per patient, no complete or partial remissions were achieved. Thirteen patients (38%) had stable disease, whereas 16 (47%) experienced progression. The median TTP was 2 months (range, 1-12 months), and the median overall survival duration was 11 months (range, 1-46 months).

Table 5. Response rates, TTP, and overall survival in phase I and II studies

Study Clinical Outcomes	Phase I	Phase II	Total
Number of patients	9	25	34
Median number of cycles (range)	4 (2-14)	2 (1-12)	2.5 (1-14)
Tumor response, n (%)			
Complete	0 (0.0)	0 (0.0)	0 (0.0)
Partial	0 (0.0)	0 (0.0)	0 (0.0)
Stable disease	7 (77.8)	6 (24.0)	13 (38.2)
Progressive disease	1 (11.1)	15 (60.0)	16 (47.1)
Non-evaluable	1 (11.1)	4 (16.0)	5 (14.7)
Median TTP (months)	5	2	2
TTP range (months)	1-12	1-6	1-12
Median overall survival duration (months)	12	10	11
OS duration range (months)	2-46	1-36	1-46

Toxicity

In the phase II study, 71 of the 76 administered cycles were evaluable for hematologic toxicity, with a median ANC nadir of 970/mcL and a median platelet count nadir of 136,000/mcL **(Table 6)**. Sixty courses were given at dose level -1, with a median ANC nadir of 1,010/mcL and a platelet count nadir of 140,000/mcL. Dose reduction was necessary in six patients who underwent 10 courses at dose level -2, with a median ANC nadir of 860/mcL and a median platelet count nadir of 70,000/mcL; another patient underwent one course at dose level -3, with a median ANC nadir of 610/mcL and a median platelet count nadir of 163,000/mcL. Grade 2 neutropenia, thrombocytopenia, and anemia were present in 20%, 13%, and 41% of cycles, respectively. Grade 3 neutropenia, thrombocytopenia, and anemia were present in 38%, 1%, and 1%. Grade 4 neutropenia occurred in 14% of the cycles, whereas no grade 4 thrombocytopenia or anemia were reported **(Table 7)**.

Table 6. Phase II number of cycles and hematologic nadirs according to gemcitabine and vinorelbine dose levels

Dose level (mg/m²)	Number of cycles	AGC nadir (range) (1,000 u/mcL)	Platelets nadir (range) (1,000 u/mcL)
All cycles	71	0.97 (0.08-6.46)	136 (41-437)
-1: G=700, V=15	60	1.01 (0.08-6.46)	140 (60-375)
-2: G=600, V=15	10	0.86 (0.21-4.21)	70 (41-437)
-3: G=500, V=15	1	0.61 (0.61-0.61)	163 (163-163)

Table 7. Incidence of NCI Common Toxicity Criteria grade 2, 3, and 4 adverse effects in phase II study (per cycle)

Toxicity	Grade, n (%)			
	2	3	4	2-4
Non-hematologic (n=76)				
Abdominal pain	1 (1.3)	1 (1.3)	0 (0.0)	2 (2.6)
Alopecia	26 (34.2)	NA	NA	26 (34.2)
Arthralgias	3 (3.9)	9 (11.8)	1 (1.3)	12 (15.8)
Constipation	9 (11.8)	1 (1.3)	0 (0.0)	10 (13.2)
Diarrhea	5 (6.6)	0 (0.0)	0 (0.0)	5 (6.6)
Fatigue	32 (42.1)	13 (17.1)	1 (1.3)	45 (59.2)
Headache	1 (1.3)	1 (1.3)	0 (0.0)	2 (2.6)
Mucositis	4 (5.3)	0 (0.0)	0 (0.0)	4 (5.3)
Myalgias	21 (27.6)	13 (17.1)	0 (0.0)	34 (44.7)
Nausea	20 (26.3)	2 (2.6)	0 (0.0)	22 (28.9)
Neutropenic fever	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.3)
Neutropenic infection	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.3)
Non-neutropenic fever	5 (6.6)	0 (0.0)	0 (0.0)	5 (6.6)
Non-neutropenic infection	1 (1.3)	1 (1.3)	0 (0.0)	2 (2.6)
Paresthesias	4 (5.3)	2 (2.6)	0 (0.0)	6 (7.9)
Rash/pruritus	4 (5.3)	1 (1.3)	0 (0.0)	5 (6.6)
Vomiting	6 (7.9)	4 (5.3)	0 (0.0)	10 (13.2)
Hematologic (n=71)				
Neutropenia	14 (19.7)	27 (38.0)	10 (14.1)	51 (71.8)
Thrombocytopenia	9 (12.7)	1 (1.4)	0 (0.0)	10 (14.1)
Anemia	29 (40.8)	1 (1.4)	0 (0.0)	30 (42.3)

The most common non-hematologic grade 2 toxicities **(Table 7)** were fatigue (42% of the cycles), alopecia (34%), myalgias (28%), nausea (26%), and constipation (12%). Grade 3 fatigue, myalgias, and arthralgias were reported in 17%, 17%, and 12% of the cycles, respectively. Grade 4 fatigue and arthralgias each occurred in one cycle (1%).

Discussion

Few chemotherapy agents or combinations have demonstrated significant activity in anthracycline- or taxane-pretreated MBC patients. Although the combination of gemcitabine and vinorelbine has not often been used in treatment, it may be an effective treatment because both agents have different mechanisms of action, with no overlapping toxicities (except for neutropenia) and only partial non-cross resistance with anthracyclines and taxanes.

Between 1999 and 2012, many phase II trials **(Table 8)** investigated the combination of gemcitabine and vinorelbine, at various dosages, in the treatment of MBC patients; the activity level was encouraging, and the toxicity profile was acceptable. In fact, response rates in phase II studies [22-39] ranged from 22.0% to 55.5%, depending on patient characteristics, drug doses and schedules, and the type of previously administered chemotherapy. TTP ranged from 3.5 to 10.8 months, and the overall survival duration ranged from 9.2 to 20 months. Toxicity was generally moderate. The major hematologic adverse effects were grade 3 or 4 neutropenia, which occurred in up to 52.0% of patients, and thrombocytopenia, which occurred in up to 20.0%. The most common grade 3 or 4 non-hematologic toxicities were nausea and vomiting (0.0% to 26.0%), constipation (0.0% to 14.0%), liver toxicity (0.0% to 10.0%), and fatigue (0.0% to 13.3%).

As a "second-line" neoadjuvant treatment in locally advanced breast cancer with no early response to docetaxel, doxorubicin, and cyclophosphamide, the combination of gemcitabine and vinorelbine was found to be both efficacious and relatively safe in a prospective phase II study conducted by Halim et al in 2011. A clinical response was achieved in 35 cases (50.0%), and a pathological response was reported in four cases (5.7%). Breast-conserving surgery became possible in 31 cases (44.0%). The most common grade 3 and 4 toxicities were neutropenia and thrombocytopenia in 25.7% and 22.8% of cases, respectively. Toxicities were reversible and did not cause death [40].

After establishing an MTD of the dose schedule investigated in phase I study (700 mg/m^2 of gemcitabine by infusion on days 1 and 8 and 15 mg/m^2 of vinorelbine by infusion on days 2 and 9, every 3weeks), we treated 25 patients in phase II to determine efficacy. Among the 21 patients evaluable for response, no complete or partial remissions were achieved. The median TTP was 2 months, and the median overall survival duration was 10 months.

These results are disappointing and are not consistent with those of any previous studies of the gemcitabine and vinorelbine combination. Three hypotheses may explain our results. First, the doses in this study were inferior to those in all but one other phase II study, in which, paradoxically, 350mg/m^2 of gemcitabine on days 1 and 8 and 25 mg/m^2 of vinorelbine on days 1 and 8 every 3 weeks resulted in a response rate of 30.4%, a TTP of 4.6 months, and an overall survival duration of 14.5 months [32].The starting doses of gemcitabine and vinorelbine that we used were based on the results of our phase I study, in which neutropenia was the major adverse effect (grade 3 or 4 neutropenia in 48% of cycles). Second, gemcitabine was administered on days 1 and 8 of the cycle and vinorelbine on days 2 and 9, whereas in most other studies, both drugs were given on days 1 and 8. Third, few previous studies included heavily pretreated MBC patients, whereas all patients in our study had undergone a median of three prior chemotherapy regimens: 97% underwent chemotherapy in the metastatic setting and 62% in the adjuvant and metastatic settings; all patients had received both anthracyclines and taxanes in the past. Consequently, our patients were more heavily pretreated than were those in most studies. Kim et al presented a similar patient profile and a response rate of 30%; however, the TTP and overall survival duration were similar to our results of 3.9 and 10.8 months, respectively [37]. The difference in the response rate may result from the increased doses (1000 vs 700 mg/m^2 of gemcitabine and 25 vs 15 mg/m^2 of vinorelbine) and the greater number of patients (57 vs 25) in Kim et al's study when compared with ours.

Grade 3 and 4 neutropenia was the major hematologic toxicity in our study, occurring in 52% of cycles and 56% of patients; this is similar to the findings of other studies, even though our doses were inferior to those of all but one other phase II study. The number of grade 3 or 4 thrombocytopenia cases, however, was minimal compared with that in other studies. As for non-hematologic adverse effects, more of our patients reported grade 3 or 4 fatigue (18% of cycles), myalgias (17%), and arthralgias (13%), but fewer experienced grade 3 or 4 constipation (1%), nausea (3%), and vomiting (5%).

The results of a few recently conducted studies are well-matched with ours. In 2007, in a phase III study, Martin et al found that anthracycline- and taxane-pretreated MBC patients treated with gemcitabine and vinorelbine had a longer progression-free

survival than did those treated with vinorelbine alone; however, there was no difference in overall survival. They also experienced more hematologic toxicities [41]. In addition, in a 2011 randomized phase II trial comparing gemcitabine plus vinorelbine, gemcitabine plus cisplatin, and gemcitabine plus capecitabine in 141 patients with pretreated MBC, similar results were found regarding treatment efficacy (overall response rates, 39.0%, 47.7%, and 34.7%; median progression-free survival durations, 5.7, 6.9, and 8.3 months; and median overall survival duration, 17.5, 13.0, and 19.4 months, respectively) and toxicity (mainly grade 3 or 4 neutropenia, 16.7%, 4.4%, and 0.0%, respectively) [42]. Pallis et al performed a multicenter randomized phase III trial of vinorelbine and gemcitabine doublet versus capecitabine monotherapy in 74 anthracycline- and taxane-pretreated women with MBC in 2011 and found that the combination was not superior in terms of progression-free survival(5.4 vs 5.2 months, respectively; p=0.736). Given the favorable toxicity and convenience of oral administration, single-agent capecitabine was recommended for compliant patients [43]. In another recent randomized phase II non-comparative study of pemetrexed-carboplatin and gemcitabine-vinorelbine for the treatment of anthracycline- and taxane-pretreated advanced breast cancer, patients experienced response rates of 26.6% and 29.5%, respectively, and a median TTP of 5.1% and 5.6%, respectively. According to the authors, both combinations, although well tolerated, showed moderate activity, as the predefined response rate was not reached [44].

Table 8. Results of phase II studies regarding the efficacy of the combination Gemcitabine and Vinorelbine in metastatic breast cancer patients between 1999 and 2012.

Study (year)	Schedule	Clinical Setting	Number of patients	Response rate (%)	Median TTP/OS (months)	WHO Grade 3/4 hematologic toxicities per patient (%)	WHO Grade 3/4 Non-hematologic toxicities per patient (%)
Haider et al[22] (1999)	G=1000 mg/m2 Days 1, 15, and 21 V=40 mg/m2 Days 1 and 21 + G-CSF *Every 5 weeks*	*First line* *Second line*	45 15	55.5 40	9.5/ >14 7.0/ 12.2	N :18 T: 0 A: 3	N/V: 5 Constipation: 3
Valenza et al[23] (2000)	G=1000 mg/m2 Days 1, 8, and 15 V=30 mg/m2 Days 1 and 8 *Every 4 weeks*	*Pretreated with Anthracyclines and taxanes*	29	48	6.8/9.2	L : 48 T : 10	None
Nicolaides et al[24] (2000)	G=1000 mg/m2 Days 1 and 8 V=30 mg/m2 Days 1 and 8 *Every 3 weeks*	*Second-line treatment after taxanes*	31	22	3.5/9.5	N: 48 T: 3	Rash: 10 Neuropathy: 3
Mariani et al[25] (2001)	G=1200 mg/m2 Days 1 and 8 V=30 mg/m2 Days 1 and 8 *Every 3 weeks*	*Pretreated except for 1 patient* *Phase I/II study*	31 (phase II)	22	ND/20 (MDR: 12)	N: 48 T: 6 A: 6	N/V: 3 Liver toxicity: 10 Constipation: 3
Sanal et al[26] (2002)	G=1200 mg/m2 Days 1 and 8 V=30 mg/m2 Days 1 and 8 *Every 3 weeks*	*Pretreated*	32	44	5/ND	L: 37.5 T: 12.5	Phlebitis: 15.6 Liver toxicity: 3.1
Stathopoulos et al[27] (2002)	G=1000 mg/m2 Day 1 V=25 mg/m2 Day 1 *Every 2 weeks*	*Pretreated with anthracyclines* *50% also treated with taxanes*	50	54	6/11.5	None	None
Donadio et al[28] (2003)	G=1000 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Pretreated with anthracyclines* *2nd or 3rd line treatment*	51	33,3	10.8/17.8	N: 11	N/V: 6
Morabito et al[29] (2003)	G=800 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Phase I/II study* *Pretreated with anthracyclines* *With or without taxanes*	50 (phase II)	42	6/>18	N: 34 A: 8	Stomatitis: 6 Liver toxicity: 2 Pain: 4
Lobo et al[30] (2003)	G=1200 mg/m2 Days 1 and 8 V=30 mg/m2 Days 1 and 8	*Pretreated at least with anthracyclines*	25	44	4.2/ND	N: 52 T: 20 A: 8	N/V: 12 Stomatitis: 4 Alopecia: 16 Infection: 12

	Every 3 weeks						Constipation: 4 Fatigue: 4 Cutaneous toxicity: 8
Dinota et al[31] (2005)	G=1000 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Advanced breast cancer in elderly patients*	34	53	ND/ND (MDR: 7-10)	N: 20 T: 11 A: 17	N/V: 26 Constipation: 14
Shmid et al[32] (2005)	G=350 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Pretreated with anthracyclines and/or taxanes*	26	30.4	4.6/14.5	N: 42 T: 11.5 A: 3.8	N/V: 3.8 Diarrhea: 3.8 Infection: 11.5 Fatigue: 3.8 Neuropathy : 3.8 Liver Toxicity : 3.8
Gemnatas et al[33] (2006)	G=1000 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Heavily pretreated with anthracyclines or taxanes*	86	36	ND/14 (MDR: 7)	N: 4.7 A: 15.1 T: 2.3	None
Morabito et al[34] (2006)	G=800 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks* + Weekly Trastuzumab (4 mg/kg on day 0, then 2 mg/kg)	*Second-line treatment HER-2/neu overexpressing MBC*	30	50	ND/15 (PFS: 7)	N: 20 T: 3.3 A: 3.3	Fatigue: 13.3
Ardavanis et al[35] (2007)	G=1000 mg/m2 Days 1 and 14 V=60 mg/m2 ORAL Days 1 and 14 *Every 4 weeks*	*Pretreated with anthracyclines* *74% also treated with taxanes*	31	35.4	5.3/14	N: 3.22 N: 3.22	N/V: 3.22
Zhou NN et al[36] (2007)	G=1000 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Previously treated with anthracyclines with or without taxanes*	34	26.47	5.4/17.8	None	None
Kim et al[37] (2008)	G=1000 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Pretreated with anthracyclines and taxanes*	57	30	3.9/10.8	N: 18.1 (of cycles) T: 0.7 (of cycles) A: 0.7 (of cycles)	Dyspnea: 0.3 (of cycles) Liver toxicity: 1.7 (of cycles)
Shehata et al[38] (2010)	Not found	*First-line treatment in MBC* *All patients previously treated with anthracyclines*	72	42	9.25/ND	N: 10 T: 1	Febrile N: 11 Nausea: 24 Stomatitis: 11 Diarrhea: 11
Dong et al[39] (2012)	G=1000 mg/m2 Days 1 and 8 V=25 mg/m2 Days 1 and 8 *Every 3 weeks*	*Elderly patients* *Pretreated with anthracyclines and taxanes*	51	33	ND/17 (PFS:6.2)	N: 25.5 T: 9.8 A: 13.7	Fatigue : 5.9 Constipation : 3.9 Neuropathy : 3.9 Liver toxicity : 3.9

Abbreviations: G- Gemcitabine, V-Vinorelbine, MBC-Metastatic breast cancer, TTP-Time to progression, OS-Overall survival, MDR-Median duration of response, PFS-progression free survival, N-Neutropenia, T-Thrombocytopenia, A-Anemia, L-Leucopenia, N/V- Nausea or vomiting, ND-Not determined

Conclusions

In MBC patients who have been heavily pretreated with both anthracyclines and taxanes, the combination of 700 mg/m^2 of gemcitabine by infusion, on days 1 and 8 and 15 mg/m^2 of vinorelbine, by infusion, on days 2 and 9 every 21 days was ineffective, as it did not induce partial or complete responses. Grade 3 and 4 neutropenia occurred in 52% of cycles, despite the lower doses of the combination compared with those in other phase II studies. Future studies should investigate the efficacy and tolerability of other chemotherapy agents or combinations in the treatment of anthracycline- and taxane-resistant MBC.

Competing Interests

The authors have declared that no competing interest exists.

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