Phase II Trial of Capecitabine and Vinorelbine as First-line Chemotherapy for Metastatic Breast Cancer Patients

MARWAN GHOSN[1], JOSEPH KATTAN[1], FADI FARHAT[2], FARIHA YOUNES[1] and JAMAL GASMI[3]

[1]*Hôtel-Dieu de France University Hospital, Beirut;*
[2]*Hammoud University Hospital Medical Center, Sidon, Lebanon;*
[3]*Institut de Recherche Pierre Fabre, Boulogne, France*

Abstract. *Background: Vinorelbine is one of the most active cytotoxic agents in metastatic breast cancer. Its association with 5-Fluorouracil generates objective responses, varying between 44 and 55%, and improves the tolerance profile. The aim of this multicenter phase II trial was to assess the combination of capecitabine and vinorelbine as first-line chemotherapy in patients with metastatic breast cancer (MBC). Patients and Methods: Thirty patients with MBC received a 3-week cycle combining capecitabine 825 mg/m^2 twice a day on days 1 through 14, with 25 mg/m^2 of vinorelbine on days 1 and 8. Treatment continued until progression, unacceptable toxicity or patient refusal to continue. The median age was 54 years (30-77) and the median WHO-PS was 1. Twenty patients (67%) received adjuvant chemotherapy including anthracycline and taxanes. Results: Objective responses occurred in 21 patients (70%). Stable disease lasting more than 6 months was observed in six patients (20%). The clinical benefit rate was 90%. The median progression-free survival and overall survival were 10 months and 30.4 months, respectively. The most frequent treatment-related toxicities were: WHO grades 3 and 4 neutropenia (two patients), febrile neutropenia (two patients), grade 3 asthenia (two patients) and grade 3 nausea/vomiting (one patient). No grade 3 hand-foot syndrome was observed. Conclusion: The combination of capecitabine and vinorelbine is an active and safe regimen for first-line treatment of MBC.*

Findings from this study have already been presented, in part, at the following conferences:

- The San Antonio Breast Cancer Symposium, San Antonio, Texas, USA, 2001.
- The European Society for Medical Oncology Congress, Nice, France, 2002.
- The 2003 ASCO meeting (Abstract 270).

Correspondence to: Marwan Ghosn, MD, Professor and Chairman, Department of Oncology-Hematology, Hôtel-Dieu de France University Hospital, Achrafieh, Blvd Alfred Naccache, P.O. Box: 166830, Beirut, Lebanon, France. Tel: 00 961 1 613 395 or 6, Fax: 00 961 1 613 397, e-mail: drghosn@sodetel.net.lb

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Despite adjuvant chemotherapy, approximately 40 to 50% of patients will develop recurrent and/or metastatic breast cancer (MBC). The average survival time from the diagnosis of metastatic disease is 18 to 30 months, although this varies according to the patient characteristics and metastatic sites (1). Systemic chemotherapy offers palliation to patients who have failed hormonal therapy or are hormonally insensitive. Combination chemotherapy is still the most commonly used palliative treatment for such patients. Several cytotoxic agents have shown consistent activity in the management of breast cancer, however the selection of first-line chemotherapy depends on several factors, including age, prior adjuvant treatment, disease-free interval, extent of the disease, co-morbidities, HER2 status and patient preference (2).

Vinorelbine, a third generation of vinca alkaloid, has demonstrated its effectiveness as an option for the treatment of MBC patients. As a single weekly agent, vinorelbine achieved impressive results in a first-line setting (3). The combination of vinorelbine with 5-Fluorouracil (5-FU) achieved high response rates of 60 to 64% and a manageable toxicity profile, though the tolerance profile of this regimen depends on the schedule (4-7). Capecitabine, an oral fluoropyrimidine that mimics 5-FU, has significant activity as a single agent or in combination with taxanes (8-11). The substitution of 5-FU by capecitabine may be more comfortable and convenient for the patient. Preclinical data have suggested that the combination of vinorelbine and capecitabine is synergistic (12). Several phase I/II trials have explored this combination in heavily pre-treated MBC patients. It has generated promising results and a satisfactory safety profile (13-16).

This phase II study was designed to contribute to knowledge regarding the efficacy and tolerability profile of a vinorelbine and capecitabine combination as first-line chemotherapy for MBC patients. The primary objective was

to evaluate the response rate to the combination. Secondary objectives included evaluation of the safety profile, progressive-free survival and overall survival.

Patients and Methods

Patient population. Eligible patients were women of at least 18 years old, with histologically proven MBC. Other inclusion criteria included a WHO performance status less than 2 and at least one bi-dimensionally measurable lesion, according to WHO criteria, that had not been irradiated. Adjuvant chemotherapy with anthracycline and taxanes as well as 5-FU was allowed. Previous hormonal therapy for adjuvant or metastatic disease was also allowed. Other requirements for eligibility were: life expectancy greater than 3 months and adequate bone marrow, liver and renal functions. Patients were required to have given written informed consent before study-specific procedures were performed and to be able to comply with the protocol for the duration of the study.

Patients were ineligible if they had local relapse only, prior chemotherapy in the metastatic setting, or had been previously treated with vinca-alkaloid or capecitabine. Patients were also excluded if they had peripheral neuropathy in more than two sites, dysphagia or inability to swallow the tablets, malabsorption syndrome or any disease significantly affecting gastro-intestinal functions that could impede the adsorption of capecitabine, other serious illnesses or medical conditions, such as cardiac disease, unstable diabetes, uncontrolled hypercalcemia, significantly active infection, or previous organ allograft. Patients who were pregnant or lactating, who had symptoms suggesting CNS or leptomeningeal metastases, who had required the concurrent use of the antiviral agent sorivudine or chemically-related analogs, who had participated in another clinical trial with any investigational drug within 30 days prior to study inclusion or who had a history of another malignancy within the previous 5 years, except cured basal cell carcinoma of the skin or excised carcinoma *in situ* of the cervix, were also excluded.

Study treatment. The chemotherapy treatment consisted of vinorelbine 25 mg/m^2 administered on days 1 and 8 of a 3-week treatment cycle, plus capecitabine 825 mg/m^2 twice daily for 14 days, *i.e.* for a daily total of 1650 mg/m^2, followed by 7 days of rest. The treatment was pursued for a minimum of eight cycles in case of response or until progressive disease, at the investigator's discretion. In case of unacceptable toxicity or patient refusal, the treatment was discontinued.

Vinorelbine was administered in a short infusion over 6 to 10 min, followed by a rapid infusion of 500 ml of normal saline. Capecitabine was taken orally within 30 min after meals twice daily at approximately the same time. The tablets were swallowed with 200 ml of water.

Dose modifications. The whole treatment regimen was delayed for 1 week in case of grade 3 or more hematological toxicity on day 1. Vinorelbine administration was cancelled on day 8 in case of grade 3 or more hematological toxicity. In case of peripheral neuropathy greater than grade 2, vinorelbine was permanently interrupted. Capecitabine dose reductions were instituted for grade 2 or 3 non-hematological toxicities or after the second appearance of grade 2 or grade 3 gastro-intestinal toxicities. If the patient experienced grade 2-3 hand-foot syndrome, the capecitabine was interrupted and reintroduced at 75% of the original dose after resolution to grade 1. In the case of a second occurrence of grade 3 hand-foot syndrome, capecitabine was interrupted and subsequently reintroduced after reduction to 50% of the original dose. In case of neutropenia grade 4, with or without fever, granulocyte colony-stimulating factor was administered in the subsequent cycles at the investigator's discretion.

Study assessments. Baseline assessments were performed in all patients within 21 days before the start of the study treatment. They included medical history, physical examination, performance status, pregnancy test if needed, ECG, chest X-rays, tumor measurements by computed tomography (CT), abdominal ultrasounds and bone scan if indicated. On day 1 of each cycle, physical condition and performance status were assessed and hematological and blood chemistry measurements were established. Additional radiological imaging was performed as clinically indicated. On day 8 of each cycle, complete blood counts were determined before vinorelbine administration.

Objective responses were assessed every 9 weeks until progression, or less than 9 weeks if early progression was suspected. The best overall response, achieved, using the standard WHO criteria of tumor response, was reported for each patient. A complete response (CR) required a complete disappearance of all previously detectable disease with no appearance of new lesions, while partial response (PR) required at least a 50% decrease of the sum of the products of the two greatest perpendicular diameters of all measurable lesions, with no appearance of new lesions or progression of any lesion. Both CR and PR had to be confirmed 4 weeks later. Stable disease (SD) was defined as less than 50% decrease or less than 25% increase in the size of one or more measurable lesions. Progressive disease (PD) was defined as 25% or more increase of previously described lesions, or the appearance of new lesions.

The efficacy analyses were based on the intent-to-treat population. The primary end-point was the overall confirmed response rate, as assessed by the investigators. Progression-free survival was defined as the interval between the date of the start of treatment and the date of progression or death, whatever the reason of death. Survival was defined as the interval between the start of treatment and the date of death. If a patient was lost to follow-up, that patient was censored at the last date of contact.

Safety was analyzed in all patients who received at least one cycle of the study medication. Adverse events were recorded throughout the study. The National Cancer Institute common toxicity criteria were used.

Results

Patient characteristics. Between April 2001 and December 2001, 30 MBC patients were enrolled in the study in three centers in Lebanon. The median age was 54 years (range: 30-77) and the median WHO-PS was 1 (range: 0-2). The estrogen-receptor and/or progesterone-receptor status, as well as Her-2/neu receptor are detailed in Table I. The most common sites of metastases were the lung, liver and bone; with 73.5% of patients having at least two metastatic sites. Twenty patients (67%) had received adjuvant chemotherapy, 17 with anthracycline-based regimen (57%) including taxanes (23%)

Table I. *Patient characteristics.*

Characteristic	No. of patients	%
No. of patients	30	-
Median age (years) (range)	54 [30-77]	-
Performance status (range)	1 [0-2]	-
ER status		
Positive	-	48
Negative	-	21
Unknown	-	31
PR status		
Positive	-	29
Negative	-	23
Unknown	-	48
Her-2/neu status*		
0 and 1+	-	33
2 +	-	17
3 +	-	10
Unknown	-	40
Prior adjuvant therapy:		
Chemotherapy	20	67
anthracycline-based	17	57
Taxanes	7	23
FU-containing	12	40
Hormonal therapy	17	57
None	5	17
Disease-free interval in months		
Mean [extremes]	37 months [0 - 154]	

*Identified by immunohistochemistry.

and 12 (40%) of the patients had received an FU-containing regimen. Seventeen patients (57%) had also received hormonal therapy in adjuvant settings. Five patients (17%) were metastatic and chemotherapy-naive at study entry (Table I). The disease-free interval from adjuvant treatment to the first metastatic relapse was 37 months (extremes: 0 to 154).

Response to treatment. Objective responses were obtained in 21 out of 30 evaluable patients (70%). Two patients (7%) achieved CRs and 19 (63%) PRs. Six patients (20%) maintained a SD (Table II). An overall clinical benefit (CR+PR+SD≥6 months) was found in 90%. These responses were observed mainly in patients with visceral metastases (68%).

The median progression-free survival was 10 months (95% CI: 7.6 to 13.6) (Figure 1) and the median survival time for all the study population was 30.4 months (Figure 2).

Dose modification. A total of 213 cycles of vinorelbine and capecitabine was administered to the 31 patients. The median number of cycles was seven (range: 1 to 13 cycles). Capecitabine dose reductions were required for seven patients, whereas the vinorelbine dose was reduced in one patient.

Table II. *Objective tumor response rate by investigator assessment.*

	No.	Response rate (%)
Complete response	2	7
Partial response	19	63
Stable disease ≥6 months	6	20
Total: Clinical benefit	27	90

Table III. *Summary of treatment-related toxicities.*

Grades 3 or 4	No.	%
Neutropenia	4	13
Asthenia	2	7
Nausea/vomiting	1	3
Diarrhea	0	0
Hand-foot syndrome	0	0

Safety. The most frequent treatment-related adverse events, regardless of severity, were asthenia, nausea, neutropenia and hand-foot syndrome. Grades 3 or 4 neutropenia was observed in four patients (however only four patients suffered from febrile neutropenia). The non-hematological toxicity was mild: eleven patients experienced grade two asthenia and only two suffered from grade 3. Only one patient had grade 3 nausea/vomiting. While no grade 3 hand-foot syndrome was observed, three patients developed grade 2 (Table III).

Discussion

The optimal management of MBC remains a great challenge for oncologists. First-line selection in the treatment of relapse has become even more complex, with increased use of anthracycline and taxanes in adjuvant settings. However, the availability of several new active chemotherapeutic agents allows for different management options. These drugs can be used in combination regimens or as single agents in sequence (2). The advantage of front-line combination chemotherapy compared to sequential single-agent therapy remains controversial. Among multiple randomized trials, there were only two studies showing a survival advantage of the combination arm over the single-agent arm. These studies assessed a combination of capecitabine / docetaxel compared to docetaxel alone (11) and combination gemcitabine / paclitaxel to paclitaxel alone (17).

Vinorelbine is one of the most active cytotoxic agents in breast cancer. It has been widely tested both as a single agent and in combination. In large phase II trials, 41% objective responses were achieved with weekly vinorelbine

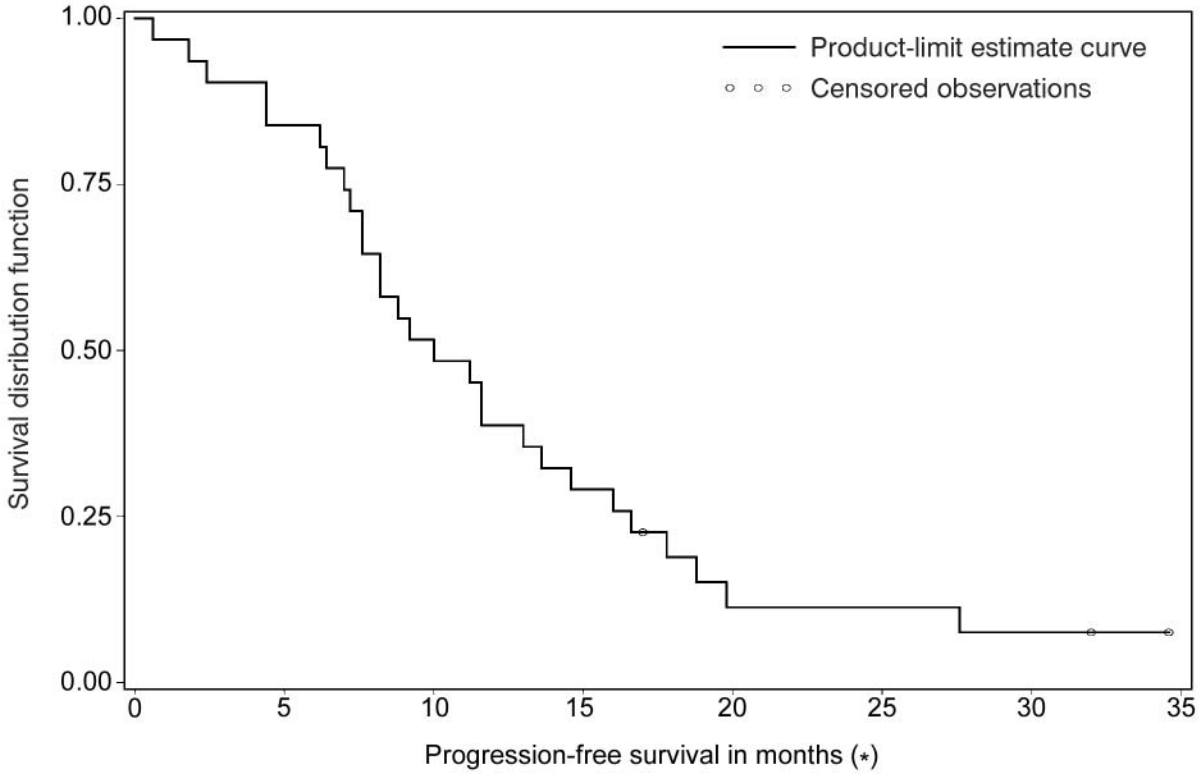

Figure 1. *Kaplan-Meier estimates for time-to-progression-free survival in intent-to-treat patients.*

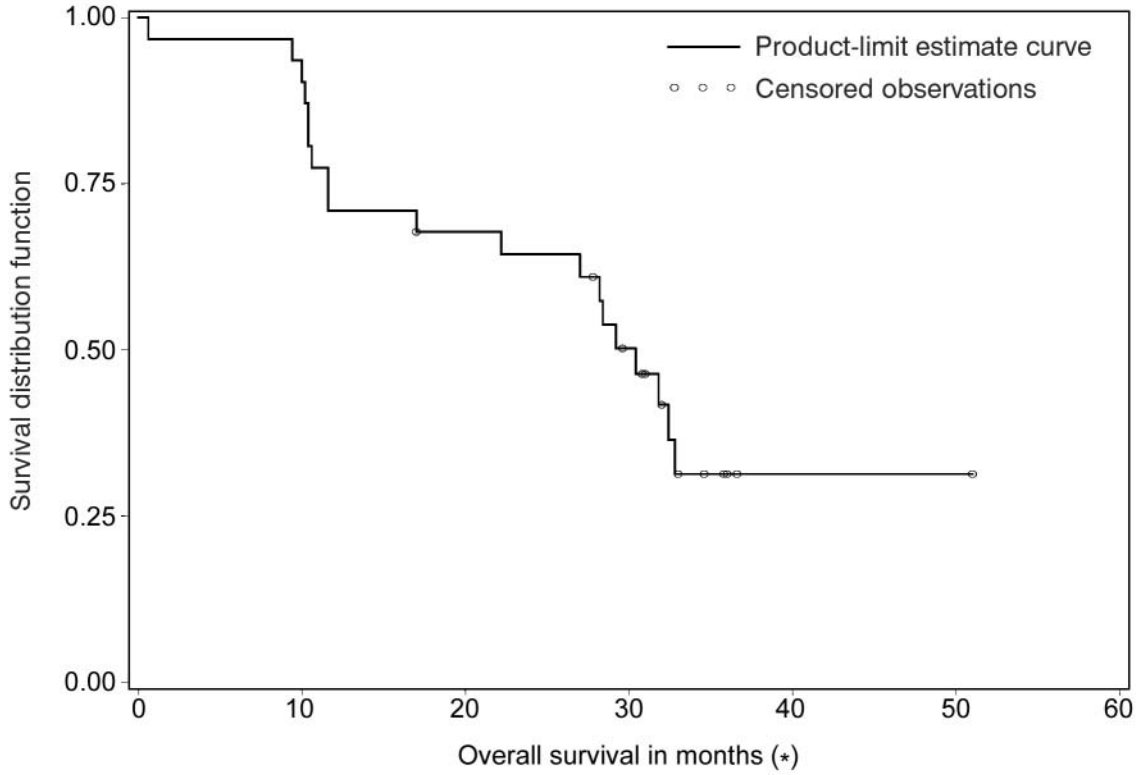

Figure 2. *Kaplan-Meier estimates for time-to-overall-survival in intent-to-treat patients.*

as first-line chemotherapy for MBC patients. Neutropenia is the main side-effect of vinorelbine use, but is generally a rapidly reversible one, leaving no complications (3). The vinorelbine /5-FU combination is the most used vinorelbine-containing regimen. This regimen is largely prescribed due to its robust efficacy and manageable safety profile. As first-line chemotherapy, this combination allowed 60 to 64% objective responses (5-7). However, the protracted continuous infusion of 5-FU using a central venous line or a peripheral access system could be the source of complications and discomfort.

Capecitabine is an oral fluoropyrimidine that mimics 5-FU, with significant activity in breast cancer. As a single agent, capecitabine has demonstrated consistent activity in first-line settings as well as after anthracycline/taxane failure (8-10). Capecitabine in combination with docetaxel has demonstrated significantly better outcomes than docetaxel alone in anthracycline-pretreated patients. However, patients receiving the combination experienced higher incidences of side-effects, mainly hand-foot syndrome, nausea/vomiting, diarrhea and mucositis, 65% requiring dose reduction (11).

Preclinical data had suggested a synergistic efficacy of capecitabine and vinorelbine (12) which led to investigations of the combination in clinical trials. Several phase II studies were conducted, mainly in heavily-pretreated patients, in which different schedules of this regimen were tested. This doublet generated respectable objective responses, varying between 44 and 55%, and improved the tolerance profile (13-16).

A combination of vinorelbine (25 mg/m^2 on days 1 and 8 every 3 weeks) and capecitabine (825 mg/m^2 twice daily on days 1 to 14 every 3 weeks) as first-line chemotherapy for MBC patients was evaluated in the present study. To our knowledge, this is the first trial testing this combination in first-line settings. This regimen showed a robust antitumor activity based on an objective response rate of 70% and clinical benefit rate of 90%. It should be noted that the median progression-free survival and median survival were 10 and 30.4 months, respectively.

The toxicity profile of this combination was predictable and manageable. As expected, neutropenia was the only treatment-related adverse event with vinorelbine and occurred at grades 3 and 4 in 10% of patients. Four patients experienced febrile neutropenia without need for hospitalization. Of note, no granulocyte-stimulating factor was needed. Hand-foot syndrome and gastro-intestinal toxicities (nausea/vomiting, diarrhea), known side-effects of capecitabine, were common but rarely severe, most probably due to the relatively reduced dose of capecitabine in our study.

These data are consistent with those recently reported in phase II and III trials of a capecitabine combined with taxanes. In a phase II study of a capecitabine and paclitaxel combination as first-line chemotherapy for MBC patients, 51% objective responses were reported for 47 assessable patients. The median time-to-disease progression and median survival were 10.6 and 29.9 months, respectively (18). Comparable outcomes have also been reported in a phase III study in which capecitabine was combined with paclitaxel or with docetaxel (19). The doses of capecitabine used in combination with taxanes were identical to those tested in our study. These doses are significantly lower than those reported in a previous large phase III trial comparing capecitabine combined with docetaxel to docetaxel alone, in which patients in the combination arm received 1250 mg/m^2 of capecitabine twice daily on days 1 to 14 every 3 weeks. Decreasing the dose of capecitabine from 1250 to 825 mg/m^2 twice daily in this trial improved the safety profile without reducing the activity.

Recently, the availability of an oral form of vinorelbine provided an alternative to the intravenous route (20). An "all oral" chemotherapy combination of vinorelbine and capecitabine has already been investigated and preliminary results are attractive (21).

In summary, our data indicate that vinorelbine at 25 mg/m^2 on days 1 and 8 combined with capecitabine at 825 mg/m^2 twice daily on days 1 to 14 every 3 weeks is a reasonable first-line treatment option for MBC patients. This regimen is active, safe and convenient, but warrants controlled studies to identify any survival advantage.

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