Phase II Study of Carboplatin, Vinorelbine and Capecitabine in Patients with Metastatic Breast Cancer

M Rabinowitz, A Mangalik, F Lee, C Jennings, A Parsons, C Verschraegen, M Royce, I Rabinowitz

Citation

M Rabinowitz, A Mangalik, F Lee, C Jennings, A Parsons, C Verschraegen, M Royce, I Rabinowitz. *Phase II Study of Carboplatin, Vinorelbine and Capecitabine in Patients with Metastatic Breast Cancer*. The Internet Journal of Oncology. 2006 Volume 4 Number 1.

Abstract

Most patients with breast cancer receive anthracyclines and taxanes in either the adjuvant or metastatic setting. Carboplatin, vinorelbine and capecitabine each has single agent activity in breast cancer. In addition they are non-cross resistant and generally have non-overlapping toxicities. The purpose of this study is to assess the response rate of this triplet combination in women with metastatic breast cancer previously treated with anthracycline and taxane based chemotherapy. The dosing schedule was carboplatin 300mg/m2 day 1, vinorelbine 25mg/m2 day 1 & 8 and capecitabine 1500mg/m2/day on days 1-14 every 21 days. Twenty three patients were evaluable for both efficacy and toxicities. Seventy eight percent of patients had refractory disease. The overall response rate was 65%. Complete responses were observed in 13%, and partial responses in 52%. The median progression free survival was 5.5 months. The Kaplan-Meier estimated median survival was 17.5 months. Two patients (8%) progressed on chemotherapy and 43% of patients received additional systemic therapy following participation in this study. Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 30%, 7% and 5% of 128 cycles, respectively. Thirty seven percent of cycles required G-CSF support. One patient died of respiratory failure, possibly related to treatment. The regimen of carboplatin, vinorelbine and capecitabine has significant activity in this refractory heavily pretreated population, making it a promising therapeutic option in women with metastatic breast cancer.

INTRODUCTION

Breast cancer remains a major cause of death for women in North America. Treatment of women with metastatic breast cancer whose disease has progressed after receiving anthracycline and taxane based chemotherapy is a common clinical dilemma. There are many potential treatment options for women with metastatic breast cancer including single agent chemotherapy, combination chemotherapy, hormonal therapy and biologic therapies, such as herceptin.

Carboplatin, vinorelbine and capecitabine have all demonstrated activity in metastatic breast cancer.[1,2,3] Capecitabine has been examined in paclitaxel refractory metastatic breast cancer and determined to have a response rate of 20%[3]. The only two grade 3-4 adverse events with an incidence of 10% or greater were hand-foot syndrome (10%) and diarrhea (14%). The doublet consisting of vinorelbine and capecitabine has also been evaluated in metastatic breast cancer patients previously treated with anthracyclines and taxanes.[4] Eighteen patients received capecitabine 1400-2250mg/m^2 for 14 days and vinorelbine 25mg/m^2 days one and eight every three weeks. The maximum tolerated dose of capecitabine was 2000 mg/m^2 x 14 days and the overall response rate was 38%.

The combination of carboplatin and vinorelbine as second line therapy in metastatic breast cancer is reported to have an overall response rate of 46% and a 46% incidence of grade 3-4 leukopenia.[5] In a separate phase I study, this combination in patients with anthracycline and taxane pretreated metastatic breast cancer resulted in a 42% incidence of grade 3-4 neutropenia and 32% grade 3-4 fatigue.[6] Of 20 patients evaluable for response, 20% had a response. Multiple studies evaluating the doublet carboplatin and vinorelbine in non-small cell lung cancer have been reported. The dosing schedules are varied, but contain vinorelbine from 25-30 mg/m^2 on days 1 and 8, with carboplatin 300-400 mg/m^2 or carboplatin AUC 4.5-7.0 day 1 every 21 days.[7,8,9,10,11,12,13]

Carboplatin, vinorelbine and capecitabine all have activity in

advanced breast cancer and they are non cross-resistant with generally non-overlapping toxicity. Thus, carboplatin, vinorelbine and capecitabine seemed a potentially promising triplet in patients with metastatic breast cancer who had previously received anthracycline and taxane based chemotherapy with progression of disease.

PATIENTS AND METHODS

PATIENT POPULATION

This single institution study was open for patient accrual between May 2000 and April 2004. Patients were to have a histological diagnosis of breast cancer with metastases. Patients were to have progressed after having received at least both anthracycline and taxane containing chemotherapy in either the adjuvant or metastatic setting. Patients could not receive concomitant hormonal, biologic or radiation therapy during the study. Patients were to have at least a three week interval between enrollment and completion of any prior radiation, hormonal therapy, biologic therapy or chemotherapy. Required laboratory data upon enrollment were absolute neutrophil count ≥1500/ μL, platelet count ≥ 100,000/ μL, creatinine ≤ 2.0 mg/dL and a bilirubin ≤ 2.0 mg/dL. An ECOG performance status of ≤ 2 was required for enrollment. Patients were required to have at least one measurable lesion. The study was approved by the local institutional review board (IRB). All patients signed an IRB approved consent form.

STUDY TREATMENT

The doses selected in this study were based on a phase I study that established the dose limiting toxicity of capecitabine at 1750 mg/m^2/day when given with carboplatin and vinorelbine.[14] Patients enrolled in this study received carboplatin 300mg/m^2 on day 1, capecitabine 1500 mg/m^2/day in divided doses, days 1 to 14, and vinorelbine 25mg/m^2 on days 1 and 8. Granulocyte-Colony Stimulating Factor (G-CSF) was allowed if there was a delay due to neutropenia.

DOSE MODIFICATION

Complete blood cell counts were obtained prior to each cycle and on day 8 before the administration of vinorelbine. For an absolute neutrophil count (ANC) of between 1000-1499/μL on day 8, the vinorelbine was decreased to 15mg/m^2 and it was held completely if the ANC was less than 1000/μL. A cycle was delayed for 1 week if on day 1 the ANC was less than 1500/μL or the platelet count was less than 100,000/ μL. G-CSF was given on days 15-20 of subsequent cycles if a treatment delay occurred due to neutropenia, or if a patient experienced neutropenic fever. Subsequently, carboplatin and vinorelbine doses were reduced if neutropenic fever occurred despite cytokine support, or for treatment delays of more than 2 weeks. Carboplatin dosing was reduced for a platelet count of less than 100,000/ L at day one of each cycle. Dose reduction levels for carboplatin: were 200mg/m^2, 100mg/m^2 and then hold. Dose reductions levels for vinorelbine were 15mg/m^2, 7.5mg/m^2 and then hold.

STATISTICAL ANALYSIS

The clinical cutoff for study analysis was July, 2004. Progression free survival and overall survival were calculated using the Kaplan-Meier method. The statistical software SPSS was used for the Kaplan-Meier calculations and graphs. Tumor response was assessed prior to every 3rd cycle of chemotherapy. The RECIST criteria were used to determine anti-tumor activity.

RESULTS

PATIENT POPULATION

Twenty three patients were enrolled from 3/2001 to 4/2004. Baseline characteristics are shown in table 1.

Figure 1

Table 1: Baseline Characteristics (N=23)

Median Age in Years (range)	51 (42-64)
Median ECOG Performance Status (range)	1 (0-2)
ER/PR Status (No. (%))	
Positive	20(87)
Negative	3 (13)
HER2neu Status	
IHC 0-1+	7
IHC 2-3+	6
Unknown	10
Metastatic sites, (% of patients)	
Liver	33
Bone	57
Lung	50
Skin/Nodal	62
1 site	22
2 sites	48
≥ 3 sites	30
Prior Chemotherapy (% of patients)	
Adjuvant Anthracycline & Taxane	43
Metastatic Anthracycline & Taxane	14
Adjuvant Anthracycline & Metastatic Taxane	43
≥ 3 prior regimens	39
mean number regimens	2.7 (range 1-7)
Prior Hormonal Therapy (% of patients)	65
mean number regimens	1.7 (range 1-3)
Percent of Patients with Refractory Disease	78

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; IHC, immunohistochemistryl.

The median length of follow up was 10 months with a range of 2 to 35 months. All patients had received prior anthracycline and taxane chemotherapy. Seventy eight

percent of patients had refractory disease, defined as a progression free interval of less than six months. Ten patients had been treated with an anthracycline in the adjuvant setting and a taxane in the metastatic setting, 10 patients had received both an anthracycline and a taxane in the adjuvant setting, and 3 patients received both an anthracycline and a taxane in the metastatic setting. Patients who had previously received an anthracycline in the past were not re-challenged with another course of anthracycline after failing a taxane. Thus it could be argued that some of these patients may not be truly refractory to both agents. The mean time from last treatment to enrollment was 5.3 months. Seventy eight percent of patients had more than one site of metastatic disease. A total of 128 cycles of chemotherapy were administered.

TOXICITY

Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 30%, 7% and 5% of cycles respectively. GCSF support was required in 37% of cycles. Thirteen percent of patients developed neutropenic fever. One patient died of presumed respiratory failure. This patient had a malignant pleural effusion with borderline respiratory function requiring supplemental oxygen prior to enrollment in the study. She had stable disease on the treatment, and had been tolerating therapy reasonably well. She had previously had a number of therapeutic thoracenteses due to respiratory difficulty. On day 12 of her 3rd cycle she had reported difficulty breathing, but declined to come in for evaluation. She died at home the following day. It was thus unclear if this was treatment related. Grade 3-4 non-hematologic toxicities were fairly uncommon and are presented in table 2.

Figure 2

Table 2: Non-hematologic Toxicity

Adverse Events	Grade 1-2		Grade3-4		Grade 5	
	No. of Pts	%	No. of Pts	%	No. of Pts	%
Death					1	4
Neutropenic Fever			3	13		
Nausea/vomiting	11	48				
Fatigue	11	48				
Peripheral neurotoxicity	9	39	1	4		
Hand-foot syndrome	9	39				
Diarrhea	5	22				
Anorexia	5	21				
Mucositis	4	17				
Constipation	4	17				
Infection	3	13	1	4		
Dizziness	2	9	1	4		
Headache	2	9				
Pain	2	9				
Depression	1	4				
Hemorrhoids	1	4				

Figure 3

Table 3: Hematologic Toxicity

Adverse Events	Grade 1-2		Grade3-4		Grade 3-4
	No. of Pts	%	No. of Pts	%	% of cycles
Anemia	17	74	5	23	7
Neutropenia	4	17	19	83	30
Thrombocytopenia	16	76	2	10	5

EFFICACY

All patients were evaluable for both efficacy and toxicities. The overall response rate was 65% (95% CI: 46-85%). Complete responses were observed in three patients (13% (95% CI: 1-27%)), partial responses in twelve patients (52% (95% CI: 31-72)). Six patients had stable disease, and two patients (8%) progressed on chemotherapy. The patients who had a complete response included a patient with subcutaneous nodules, a patient with skin nodules, and a patient with pulmonary and nodal involvement. Of the patients with a partial response, 8 had visceral disease in the liver and/or lung, and 4 had only skin and/or nodal disease. The median progression free survival was 5.5 months (95% CI: 3.7-7.2). The Kaplan-Meier estimated median survival was 17.5 months (95% CI: 6– 28). Forty three percent of patients received additional systemic therapy following participation in this study.

Figure 4

Figure 1: Kaplan-Meier plot for progression free survival

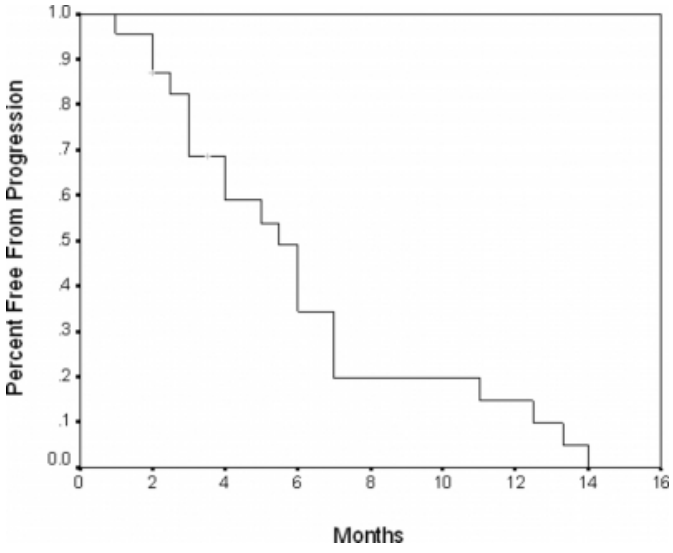
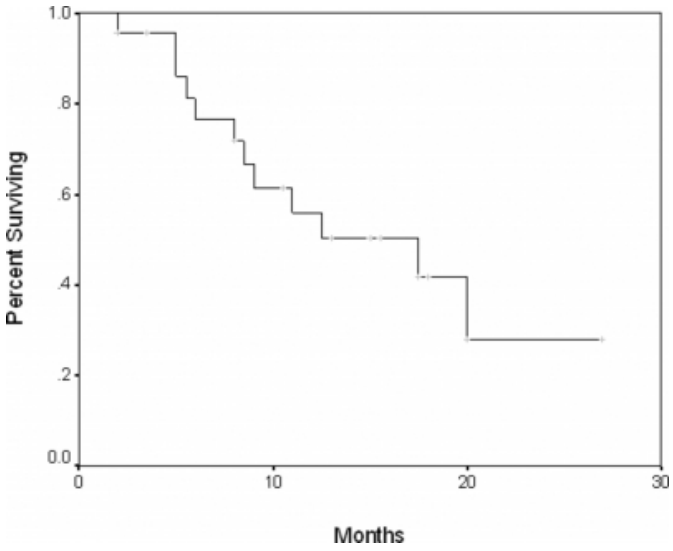


Figure 5

Figure 2: Kaplan-Meier plot of overall survival



DISCUSSION

This small phase II study demonstrates that the combination of carboplatin, vinorelbine and capecitabine is an active regimen in women with metastatic breast cancer previously treated with anthracyclines and taxanes. The side effects of this triplet are predictable and manageable. Grade 3-4 non-hematologic toxicities were uncommon. Grade 3-4 hematologic toxicities were frequent, with 83% of patients experiencing grade 3-4 neutropenia. However, only three patients experienced neutropenic fever and very few cycles resulted in grade 3-4 anemia or thrombocytopenia (7% and 5% respectively). The response rate in this study is much higher than that of the combinations carboplatin and vinorelbine $(20\%)_5$ or capecitabine and vinorelbine $(38\%)_{4,\ 13}$ in women with anthracycline and taxane pretreated metastatic breast cancer. Furthermore the progression free survival was relatively robust at 5.5 months. This suggests that this regimen may exhibit synergy. However, given that this is a small phase II study, the data must be interpreted with caution.

The role of combination chemotherapy in the setting of metastatic breast cancer is uncertain. The increased response rate seen with combination therapy is offset by increased toxicity. Many patients may benefit from sequential rather than combination chemotherapy. However, this regimen may be useful in a subset of patients with significantly symptomatic disease that necessitates a high probability of disease response to treatment. The population in this study consisted primarily of women with aggressive disease, as indicated by the short interval between last treatment and enrollment. The patients who had received an anthracycline in the adjuvant setting and then relapsed, could have been re-challenged with another course of anthracycline containing chemotherapy to confirm refractoriness to an anthracycline. It is not our practice to repeat anthracyclines in this setting and thus we cannot rule out the possibility that a certain percentage of the 43% of patients falling into this group were in fact not anthracycline refractory. Nevertheless, in this population with primarily refractory disease, the combination of carboplatin, vinorelbine and capecitabine still yielded a 65% response rate. We feel that this combination is one of the more active combinations in the metastatic setting. However, as stated above, the decision to use a sequential approach or a combination approach in the treatment of patients with metastatic breast cancer needs to be tailored to the individual patients' clinical situation.

Perhaps the most significant aspect of this study is its potential use in the adjuvant setting. It is presently unclear what to do with patients who, despite neoadjuvant anthracycline and taxane containing chemotherapy, still have significant residual disease in the surgical mastectomy or lumpectomy specimen. Clearly their risk of relapse is high, but at the present time there is no regimen found to be effective in improving these patients risk of relapse. It is conceivable that a regimen with a high non cross-resistance to the neoadjuvant chemotherapy may be considered in such patients. If the results described here can be reproduced, a regimen of carboplatin, capecitabine and vinorelbine could be tested in this setting.

CORRESPONDENCE TO

University of New Mexico Cancer Research and Treatment Center 900 Camino de Salud, NE MSL 09-4630 Albuquerque, NM 87131 Telephone: (505) 272-4946 FAX: (505) 272-6668 e-mail: irabinowitz@salud.unm.edu

References

1. O'Brien M, Talbot D, Smith I. Carboplatin in the treatment of advanced breast cancer: a phase II study using a pharmacokinetically guided dose schedule. Journal of Clinical Oncology 1993;11(11):2112-7.
2. Romero A, Rabinovich M, Vallejo C, et al. Vinorelbine as first-line chemotherapy for metastatic breast carcinoma. Journal of Clinical Oncology 1994;12(2):336-41.
3. Blum J, Jones S, Buzdar AU, et al. Multicenter Phase II Study of Capecitabine in Paclitaxel-Refractory Metastatic Breast Cancer. Journal of Clinical Oncology 1999;17(2):485.
4. Lorusso V, Crucitta E, Silvestris N, et al. A phase I study of capecitabine in combination with vinorelbine in advanced breast cancer. Clinical Breast Cancer 2003;4(2):138-41.
5. Iaffaioli R, Tortoriello A, Facchini G, et al. A phase II study of carboplatin and vinorelbine as second-line treatment for advanced breast cancer. British Journal of Cancer 1995;72(5):1256-8.
6. Kosmas C, Agelaki S, Giannakakis T, et al. Phase I study of vinorelbine and carboplatin combination in patients with taxane and anthracycline pretreated advanced breast cancer. Oncology 2002;62(2):103-9.
7. Garst J, Crawford J, O'Rouke M, et al. Vinorelbine and carboplatin for the treatment of patients with advanced NSCLC: a phase II response, toxicity and survival study. Proc. Am. Soc. Clin. Oncol. 1996;15:1233a.
8. Gridelli C, Perrone F, GP GI, et al. Carboplatin plus vinorelbine, a new well-tolerated and active regimen for the treatment of extensive-stage small-cell lung cancer: a phase II study. Journal of Clinical Oncology 1998;16(4):1414-9.
9. Masotti A, Borzellino G, Zannini G, et al. Efficacy and toxicity of vinorelbine-carboplatin combination in the treatment of advanced adenocarcinoma or large cell carcinoma of the lung. Tumori 1995;81:112-6.
10. Cremonesi M, Mandala M, Cazzaniga M, Rezzani C, Gambera M, S SB. Vinorelbine and carboplatin in inoperable non-small cell lung cancer: a monoinstitutional phase II study. Oncology 2003;64(2):97-101.
11. Jacoulet P, Breton J, Westeel V, et al. Phase I study of vinorelbine and carboplatin in advanced non-small cell lung cancer. Lung Cancer 1995;12:247-57.
12. Colleoni M, Boni L, Vicario G, et al. A dose-escalating study of carboplatin combined with vinorelbine in non-small-cell lung cancer. Oncology 1996;53:364-8.
13. Santomaggio C, Tucci E, Rinaldini M. Carboplatin and vinorelbine in the treatment of advanced non-small-cell lung cancer: a multicenter phase II study. Am J Clin Oncol 1998;21:67-71.
14. Donaldson L, Jennings C, Lee F, Mangalik A, I Rabinowitz. A phase I/II study of carboplatin, vinorelbine and capecitabine in patients with metastatic breast cancer. Proc. Am. Soc. Clin. Oncol. 2002:1960.

Author Information

Max Rabinowitz, M.D.
University of New Mexico Cancer Research and Treatment Center

Aroop Mangalik, M.D.
University of New Mexico Cancer Research and Treatment Center

Fa-Chyi Lee, M.D.
University of New Mexico Cancer Research and Treatment Center

Carla Jennings, R.N.
University of New Mexico Cancer Research and Treatment Center

Ann Parsons, R.N.
University of New Mexico Cancer Research and Treatment Center

Claire Verschraegen, M.D.
University of New Mexico Cancer Research and Treatment Center

Melanie Royce, M.D., Ph.D.
University of New Mexico Cancer Research and Treatment Center

Ian Rabinowitz, M.D.
University of New Mexico Cancer Research and Treatment Center