

Capecitabine and Vinorelbine in Patients with Metastatic Breast Cancer Previously Treated with Anthracycline and Taxane

We have evaluated the efficacy and safety of the combination of capecitabine and vinorelbine in metastatic breast cancer (MBC) patients previously treated with anthracycline- and taxane-containing regimens. Between April 2000 and September 2002, 44 female MBC patients received oral capecitabine (1,250 mg/m² twice daily on days 114), and intravenous vinorelbine (25 mg/m² on days 1 and 8) during each 3 week-chemotherapy cycle (median, 5 cycles/patient; total, 235 cycles). One patient achieved a complete response and 21 patients had partial responses, giving an overall response rate of 50% in the intention-to-treat analysis (95% CI, 35.0-65.0%). Median duration of response was 6.0 months (range 1.2-23.0 months). Patients were followed-up for a median of 16 months, with median progression-free survival being 5.3 months, and median overall survival being 17 months. Toxicities included grades III and IV neutropenia in 63 (26.8%) and 4 (1.7%) cycles, respectively, and grades II and III hand-foot syndrome in 12 (5.1%) and 4 (1.7%) cycles, respectively. Other nonhematologic toxicities were minimal and manageable. In conclusion, the combination of capecitabine and vinorelbine was effective and well tolerated in MBC patients even after treatment with anthracyclines and taxanes.

Key Words : Breast Neoplasms; Drug Therapy; Antineoplastic Combined Chemotherapy Protocols; Capecitabine; Vinorelbine

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INTRODUCTION

Metastatic breast cancer (MBC), one of the most common cancers affecting women, is regarded as largely incurable (1). Many chemotherapeutic agents have shown antitumor activity in MBC, among which the anthracyclines have been considered standard therapy (2, 3). Recently, taxanes have been reported to have efficacy in treating patients with MBC including individuals previously treated with anthracyclines (4). Few treatment options are available, however, for patients with MBC who have failed both anthracycline- and taxane-based chemotherapy regimens, or who face increased risk of developing anthracycline toxicity from further cumulative doses. Due to the poor overall outcome for patients with MBC, the aim of salvage chemotherapy is palliation of symptoms and improvement of quality of life. Thus, active agents with minimal toxicity are required for these patients.

Vinorelbine, a semisynthetic vinca alkaloid, has been considered one of the most active cytotoxic drugs against MBC, with a low toxicity profile. Vinorelbine has been found to yield response rates of 34-50% as a single agent when used

as first-line therapy, and 15-30% as second-line therapy (5-11). The combination of vinorelbine and infused 5-fluorouracil (5-FU) has been acknowledged as an effective palliative regimen for MBC, especially in Europe, and has been tested in several phase II studies (12-15). Although this regimen showed high response rates, up to 70%, as first-line therapy, treatment tolerance was not satisfactory.

Capecitabine (Xeloda[®]), a fluoropyrimidine carbamate, was developed as an orally active agent that would deliver 5-FU selectively to the tumor tissues, and that would replace the more cumbersome infused 5-FU. In phase I/II studies, capecitabine gave response rates of 20-30% in patients with paclitaxel-refractory MBC, along with minimal bone marrow suppression (16-18). Capecitabine is also suitable for combination with a variety of agents, particularly those known to further upregulate thymidine phosphorylase (TP) in tumor tissue, such as paclitaxel, taxotere, and mitomycin-C (19-21). Several phase I/II studies using combinations of capecitabine and taxanes have demonstrated the high efficacy and safety of these regimens in MBC (22-24). Recently, data from a xenograft model indicated synergistic activity of capecitabine

and vinorelbine by upregulation of TP in tumor tissue (25).

Due to their different mechanisms of anti-tumor activity, their differing toxicity profiles, and synergistic effect of both drugs, the combination of capecitabine and vinorelbine would be a reasonable choice for chemotherapy of MBC. There have been few reports, however, on this combination regimen although several phase I or II studies are ongoing (26-29).

We have had some experience with 3 week cycles of oral capecitabine (2,500 mg/m²/day on days 1-14) and intravenous vinorelbine (25 mg/m²/day on days 1 and 8) as last-line treatment in MBC. We found that this regimen was effective and well tolerated, although some patients could not receive the day 8 dose of vinorelbine due to myelosuppression. We therefore performed a prospective study to see the efficacy and safety of this combination chemotherapy in MBC patients previously treated with both anthracycline- and taxane-containing regimens. Preliminary results of this study were previously published in an abstract form (30).

MATERIALS AND METHODS

Patient Selection

Between April 2000 and September 2002, female patients with MBC were enrolled if they had measurable disease [i.e. a tumor having at least one diameter ≥ 2 cm by clinical examination, chest radiography or conventional computed tomography (CT) scan], or assessable disease, which was difficult to measure but could be evaluated grossly [i.e. by having diffuse small and numerous metastases in the liver or lung, or bone metastases]. All patients were ≥ 20 yr of age, had a performance status of 0-2 on ECOG scale, and had a life expectancy of at least 3 months. All patients were previously treated with anthracycline- and taxane-containing regimens, to which the disease was primarily refractory, or the patients relapsed after initial response. All patients had adequate hematologic function (absolute neutrophil count (ANC) $\geq 1,500/\mu\text{L}$, platelet count $\geq 75,000/\mu\text{L}$), hepatic function (total bilirubin

Table 1. Capecitabine dose modification for non-hematologic toxicities

NCI CTC toxicity grade	Appearance	Adjust during therapy	Adjustment for next cycle (%)
Grade 2	1st	Interrupt until resolved to grade 0 or 1	100
	2nd	Interrupt until resolved to grade 0 or 1	75
	3rd	Interrupt until resolved to grade 0 or 1	50
	4th	Discontinue treatment	
Grade 3	1st	Interrupt until resolved to grade 0 or 1	75
	2nd	Interrupt until resolved to grade 0 or 1	50
	3rd	Discontinue treatment	
Grade 4	1st	Interrupt until resolved to grade 0 or 1	50
	2nd	Discontinue treatment	

≤ 2.0 mg/dL, serum transaminase ≤ 3 times the upper normal limit (UNL) or ≤ 5 times UNL in cases with hepatic metastases), and renal function (serum creatinine ≤ 1.5 mg/dL). Patients who had received high dose chemotherapy and stem cell transplantation were eligible.

Exclusion criteria included patients who were pregnant or lactating, those with central nervous system metastases, patients with a prior history of other cancers within the previous 5 yr, aside from basal cell or squamous cell carcinoma of the skin, or carcinoma in situ of the uterine cervix, and those with significant gastrointestinal disease that could cause significant malabsorption or could affect drug intake. Patients could not have received chemotherapy, hormonal therapy or radiotherapy less than 4 weeks before study entry. The protocol was approved by the Institutional Review Board of Asan Medical Center. All patients gave written informed consents.

Table 2. Patient characteristics

	No. of patients
No. of patients	44
Age, years, median (range)	45 (29-75)
ECOG performance status	
0/1/2	25/14/5
ER or PR receptor status*	
Positive	17 (38.6%)
Negative	17 (38.6%)
Unknown	10 (22.7%)
Prior treatment	
Adjuvant radiotherapy	17
Hormonal therapy	21
Anthracyclines	
Adjuvant chemotherapy	14
Palliative chemotherapy	30 (refractory cases 18)
Taxanes	
Palliative chemotherapy	44 (refractory cases 29)
High dose chemotherapy with stem cell support	2
Number of previous chemotherapy regimens, median	2 (1-3)
DFI [†] after curative surgery, months, median (range)	20 (6.3-180)
Number of metastasis sites, median (range)	2 (1-4)
Measurable disease/Assessable disease alone	26/18
Dominant metastatic sites	
Measurable disease	38
Lung	2
Liver	7
Lymph nodes (axilla, neck, mediastinal LN)	17
Chest wall or breast mass	12
Assessable disease	50
Bone	24
Pleural/ pericardial effusion	6 (5/1)
Disseminated lung metastasis	11
Disseminated liver metastasis	5
Diffuse chest wall metastasis	3
Peri-pyloric metastasis	1

*estrogen receptor/progesteron receptor; [†]disease-free interval.

Treatment schedule

Each 3-week cycle of chemotherapy consisted of oral capecitabine (1,250 mg/m² twice daily), according to the standard intermittent schedule (2 weeks of treatment followed by a 1-week rest period), plus intravenous vinorelbine, infused within 5-10 min at a dose of 25 mg/m² on days 1 and 8 of each 3-week treatment cycle. Prophylactic colony stimulating factor was not permitted. Duration of treatment was based on response, and the study was initially designed so that patients with objective responses or stable disease would continue to receive chemotherapy unless the disease progressed or unacceptable toxicities occurred. Due to financial and insurance problems, however, patients who maintained a tumor response or stable disease beyond 6 cycles of chemotherapy were allowed an interruption and observation.

Palliative radiotherapy was not allowed until progression.

Toxicities and dose modification

Toxicity was graded before each treatment cycle according to the National Cancer Institute of Common Toxicity Criteria (31). The capecitabine dose was adjusted for non-hematological toxicities as outlined in Table 1. Dose adjustment criteria for vinorelbine was based on hematologic toxicities evaluated on days 1 and 8 of each cycle. If grade II neutropenia or thrombocytopenia had occurred on day 8, the vinorelbine dose delivered that day was reduced by 50%, whereas, if grade III/IV neutropenia or thrombocytopenia occurred, vinorelbine was not administered. If neutropenia greater than grade I had occurred on day 1, the treatment cycle was delayed for one week and then resumed at the same dose after resolution to grade I or better. If day 1 chemotherapy with either drug was delayed due to toxicity, administration of the other was also delayed, such that capecitabine and vinorelbine were started together on the same day of each cycle.

Pretreatment and follow-up evaluation

Prior to the first cycle of chemotherapy, each patient under-

went a baseline assessment, including a complete medical history and physical examination, chest radiography, liver ultrasonography, and bone scan. CBC was performed on days 1 and 8 of each cycle, and blood chemistry tests were performed on day 1 of each cycle. Compliance for administration of capecitabine was monitored by questioning patients at each outpatient visit and counting their remaining pills at each cycle.

Response evaluation

In patients with measurable disease, response was assessed every 3 cycles using standard WHO criteria. The measurable disease by physical examination was assessed at each cycle. Complete response (CR) was defined as the disappearance of all known diseases, whereas partial response (PR) was defined as a 50% reduction of measurable disease. Progressive disease (PD) was defined as a 25% increase of measurable disease or the development of new lesions, and all other outcomes were assessed as stable disease (SD).

In patients with assessable disease, response was assessed when follow-up imaging studies showed obvious decrease in size and/or number of lesions, as judged by radiologists, and by improvement of symptoms. Response was categorized as improved, stable, or progressed.

Statistical analysis

The primary end point was response rate, and all eligible patients were included in the intention-to-treat (ITT) analysis of efficacy. This study was designed such that the expected response rate was 40% and so that the study would be halted if the response rate was 20% or less. According to Simon's two stage phase II design with α and β errors of 0.05 and 0.20, respectively, a minimum of 13 patients would be required to terminate the study as early as possible if the response rate was 20% or less for the first stage of the study ($\leq 3/13$). Otherwise, 43 patients would be required, and the study would

Table 3. Antitumor activity

Response*	Measurable disease (n=26)	Response	Assessable disease (n=18)
CR	1 (3.8%)		
PR	13 (50.0%)	improved	8 (44.4%)
SD	4 (15.4%)	stable	5 (27.8%)
PD	7 (26.9%)	progressed	5 (27.8%)
Not evaluated	1 (3.8%)		

Overall response rate 50.0% (22/44) (95% CI, 35-65%)
 Response duration; median 6.0 months (range 1.2-23.0 months)

*CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Response rates according to metastatic sites

Measurable diseases	Number	Response	CR	PR	SD
Lung	2	2 (100%)		2	
Liver	7	3 (42.9%)		3	2
Lymph nodes	17	10 (58.8%)	6	4	3
Chest wall/breast	12	6 (50.0%)		6	4
Assessable disease	Number	Improved	Stable		
Lung	11	3 (27.3%)	4		
Liver	5	2 (40.0%)			
Bone	24	3 (12.5%)	10		
Malignant effusion	6	4 (66.7%)	1		
Diffuse chest wall	3	0 (0%)	3		
Peri-pyloric mass	1	0 (0%)	1		

CR, complete response; PR, partial response; SD, stable disease.

be terminated if 12 or fewer responded to this regimen. Since we expected a non-compliance rate of 10%, we planned to enroll a total of 48 patients.

Progression-free survival (PFS), overall survival (OS) and duration of response were estimated as secondary end-points by the Kaplan-Meier method. The duration of response was measured from the date of documented response to the onset of PD; PFS times were determined from the date of entry to the study to the date of PD or death; and OS was measured from the date of entry to the date of last follow-up or death.

RESULTS

Patient characteristics

Between April 2000 and September 2002, 48 patients were enrolled into the study. Four of these patients were found to be ineligible: two had brain metastases, one did not have baseline data prior to the start of chemotherapy, and one patient

Table 5. Toxicity (NCI common toxicity criteria) of total 235 cycles

Toxicity	Grade I	Grade II	Grade III	Grade IV
Hematologic				
Neutropenia*	38 (16.2%)	68 (28.9%)	63 (26.8%)	4 (1.7%)
Anemia	121 (51.5%)	35 (14.9%)	7 (3.0%)	0 (0%)
Thrombocytopenia	7 (3.0%)	6 (2.6%)	2 (0.9%)	0 (0%)
Nonhematologic				
Nausea/ Vomiting	63 (26.8%)	7 (3.0%)	1 (0.5%)	0 (0%)
Stomatitis	45 (19.1%)	22 (9.4%)	2 (0.9%)	0 (0%)
Diarrhea	15 (6.4%)	2 (0.9%)	0 (0%)	0 (0%)
Neuropathy	123 (52.3%)	8 (3.4%)	0 (0%)	-
Hand-Foot syndrome	51 (21.7%)	12 (5.1%)	4 (1.7%)	-
Hepatotoxicity				
Transaminase	48 (20.4%)	8 (3.4%)	0	0
Bilirubin	14 (6.0%)	1 (0.5%)	0	0

*Febrile neutropenia: only 1 episode in 1 patient.

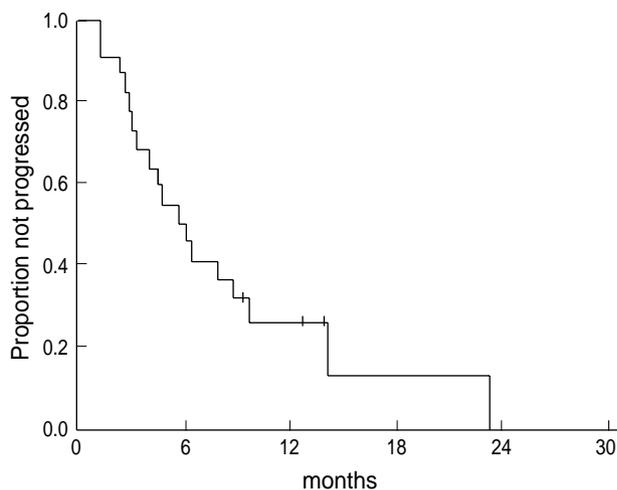


Fig. 1. Response duration for 22 responders (median, 6.0 months; range, 1.2-23.0 months).

showed very poor performance status (ECOG >2). The characteristics of the remaining 44 patients are shown in Table 2. The median age of all patients was 45 yr (range, 29-75 yr). Twenty-six patients had measurable disease, whereas 18 patients had only assessable disease. Combination therapy for metastatic disease was administered to 22 patients as second-line treatment, 19 as third-line treatment, and 3 as fourth-line treatment. A total of 235 cycles were administered (median, 5 cycles per patient; range, 1-24). All 44 patients were evaluable for toxicity and 43 patients for response, with 1 patient refusing evaluation of response after 3 cycles of chemotherapy.

Efficacy and survival

ITT analysis was applied to assess the response rate in all 44 patients (Table 3). Among the 26 patients with measurable disease, CR was observed in 1 (3.8%) with lung and neck lymph node metastases, and PR in 13 (50%), yielding an objective response rate of 53.8%. Among the 18 patients with assessable disease alone, 8 patients (44.4%) had improvement of symptoms with an obvious tumor response by imaging studies. Thus, the overall response rate in the ITT population of 44 patients was 50.0% (22/44, 95% CI, 35.0-65.0%). Response rates according to the metastatic sites are listed in Table 4.

The median follow-up time was 16 months, and their median duration of response was 6.0 months (range, 1.2-23.0 months) (Fig. 1). The median PFS time was 5.3 months in all patients (range, 1.0-30 months) (Fig. 2) and median OS time was 17 months (range, 1.8-30.0+ months).

Toxicity and dose intensity

We found that, during the 235 cycles of chemotherapy, hematologic toxicity was the most common adverse reaction

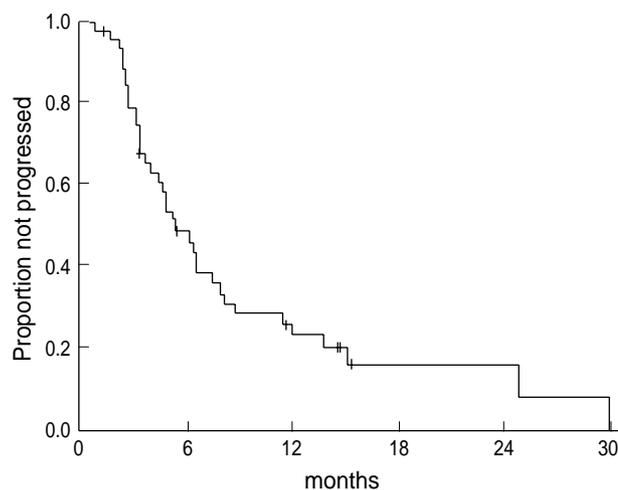


Fig. 2. Progression-free survival for all patients (median, 5.3 months; range, 1.8-30.0 months).

with grades III and IV neutropenia observed in 63 (26.8%) and 4 (1.7%) cycles, respectively, and in 30/44 (68.2%) patients. Only 1 patient, however, had febrile neutropenia, which was quickly reversible. There were no other admissions to the hospital for the treatment of infections or other toxicities. Grades II and III hand-foot syndrome occurred in 16 (6.8%) cycles, and in 10 (22.7%) of patients. Other nonhematologic toxicities were minimal and manageable (Table 5).

The dosage of capecitabine had to be reduced in 18 cycles of 11 patients due to grade II or III hand-foot syndrome (12 cycles) or grade II or III stomatitis (6 cycles). Dose reduction of vinorelbine on day 8 was required during 75 cycles (31.9%), 68 for grade II neutropenia, 4 for grade II/III stomatitis, and 3 for neurotoxicity. Vinorelbine on day 8 could not be given during 50 cycles (21.3%), 46 for grade III/IV neutropenia, 3 for poor vein status, and 1 for another reason. Chemotherapy had to be delayed in 82/235 (34.9%) cycles, primarily due to hematologic toxicity (65 cycles), but it was delayed for personal reasons in 15 cycles and for hand-foot syndrome in two. The median relative dose of capecitabine was 81.3% (range, 47-100%), whereas that of vinorelbine was 68.0% (range, 38-100%) of the planned doses.

DISCUSSION

With the widespread use of anthracyclines as adjuvant chemotherapy or first-line treatment of MBC and taxane-based regimens as salvage treatment, medical oncologists face difficulties in deciding how to treat MBC patients previously treated with these drugs. We have shown here that the combination of capecitabine and vinorelbine is highly active, achieving objective responses of 50% and a median response duration of 6 months in patients who had undergone both anthracycline- and taxane-based regimens. This response rate is very encouraging in this group of patients.

We found that although neutropenia was a frequent adverse event of this treatment regimen, it was relatively mild, with grade III occurring during 26.8% of cycles and grade IV during 1.7%, and, febrile neutropenia occurring only once in 1 patient. In addition, while hand-foot syndrome occurred in 24 (54.5%) patients and during 67 (28.5%) cycles, grade III toxicity occurred only during 4 cycles. Other non-hematologic toxicities were also minimal, and our patients went through treatment without serious complications, although dose modifications were necessary. Our findings indicate that this regimen was much less toxic than other regimens, including the combinations of adriamycin and cyclophosphamide, and adriamycin and taxane, as well as any combinations that include platinum.

Relative to the planned doses, the median relative dose of vinorelbine was 68.0% and that of capecitabine was 81.3%. The median dose intensity of capecitabine in our study did not differ much from the 77% observed during combination

treatment with capecitabine and docetaxel (32). In that study, the combination of capecitabine and docetaxel achieved a response rate of 42% and a median time to progression of 6.1 months, as well as better survival than observed with docetaxel alone. And dose modification of capecitabine did not have a negative effect on response rate. A recent phase II study reported a response rate of 40% with the combination of capecitabine (2,000 mg/m²/day for 2 weeks) and vinorelbine (25 mg/m² on days 1 and 8) in MBC patients previously treated with anthracycline and/or taxane (26). These data suggest that it may be possible to reduce the dose of capecitabine when it is combined with vinorelbine. In addition, our finding of a 50% response rate with a 68% relative dose intensity of vinorelbine, and, in many cases, the elimination of the day 8 doses, suggests that the dose of vinorelbine can also be reduced in heavily pretreated patients.

In our protocol, the dosage of vinorelbine was to be reduced by 50%, instead of 25%, on day 8 for grade II neutropenia, and no vinorelbine was to be given on day 8 in patients with grade III neutropenia. This is a somewhat aggressive dose modification. Although the proper dose schedule of this regimen was not clearly determined during the previous phase I studies, capecitabine 2,000 mg/m²/day for 2 weeks and vinorelbine 25 mg/m²/days 1 and 8 every 3 weeks has been generally recommended in this setting (27-29). A recent phase II study using this dose schedule showed, however, that treatment delay or dose reduction due to myelosuppression was common, resulting in reductions of dose intensity of capecitabine to 78% and vinorelbine to 82% of planned doses (26).

Our study included patients who had been previously treated with several chemotherapy regimens, suggesting that use of capecitabine and vinorelbine as first-line treatment for MBC may result in greater tolerability and less hematologic toxicity, as well as a better response rate than ours. Among the commonly used first-line regimens are adriamycin and paclitaxel (AT), fluorouracil, adriamycin and cytoxan (FAC), and adriamycin and cytoxan (AC), which have been reported to have response rates of 54-68% (33, 34). These regimens, however, have been associated with grade IV neutropenia in 27-89% of patients, and febrile neutropenia in 5-32% of patients, much higher rates than we observed here with capecitabine and vinorelbine. Since our regimen was very effective and had a low toxicity profile as a second or third line treatment, it would be of interest to determine whether a better response rate would be obtained if one moves our regimen up one step to be tried on patients previously treated with anthracycline but not taxane, and then compare this regimen to the combination of capecitabine and docetaxel. It would also be of interest to determine the efficacy of our regimen as a first-line treatment. The results shown here indicate that, even as a second or third line treatment, the combination of capecitabine and vinorelbine has merit for patients with MBC who cannot tolerate the severe toxicity of other treatment regimens.

In conclusion, we have shown here that, in treating MBC,

the combination of capecitabine and vinorelbine is very effective and has low toxicity as a second or third line treatment.

REFERENCES

- Greenlee RT, Hill-Harmon MB, Murray T, Thun M. *Cancer statistics, 2001. CA Cancer J Clin* 2001; 51: 15-36.
- Tormey C. *Adriamycin (NSC 123-127) in breast cancer. An overview of studies. Cancer Chemother Rep* 1975; 3: 319-27.
- Stewart DJ, Evans WK, Shepherd FA, Wilson KS, Pritchard KI, Trudeau ME, Wilson JJ, Martz K. *Cyclophosphamide and fluorouracil combined with mitoxantrone versus doxorubicin for breast cancer: Superiority of doxorubicin. J Clin Oncol* 1997; 15: 1897-905.
- Perez EA. *Paclitaxel in breast cancer. Oncologist* 1998; 3: 373-89.
- Budman DR. *Vinorelbine (Navelbine): A third-generation vinca alkaloid. Cancer Invest* 1997; 15: 475-90.
- Johnson SA, Harper P, Hortobagyi GN, Pouillart P. *Vinorelbine: An overview. Cancer Treat Rev* 1996; 22: 127-42.
- Smith GA. *Current status of vinorelbine for breast cancer. Oncology* 1995; 9: 767-73.
- Romero A, Rabinovich MG, Vallejo CT, Perez JE, Rodriguez R, Cuevas MA, Machiavelli M, Lacava JA, Langhi M, Romero Acuna L. *Vinorelbine as first-line chemotherapy for metastatic breast carcinoma. J Clin Oncol* 1994; 12: 336-41.
- Fumoleau P, Delgado FM, Delozier T, Monnier A, Gil Delgado MA, Kerbrat P, Garcia-Giralte E, Keiling R, Namer M, Closon MT. *Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. J Clin Oncol* 1993; 11: 1245-52.
- Twelves CJ, Dobbs NA, Cumow A, Coleman RE, Stewart AL, Tyrrell CJ, Canney P, Rubens RD. *A phase II multicentre, UK study of vinorelbine in advanced breast cancer. Br J Cancer* 1994; 70: 990-3.
- Weber BL, Vogel C, Jones S, Harvey H, Hutchins L, Bigley J, Hohneker J. *Intravenous vinorelbine as first-line and second-line therapy in advanced breast cancer. J Clin Oncol* 1995; 13: 2722-30.
- Dieras V, Extra JM, Bellissant E, Espie M, Morvan F, Pierga JY, Mignot L, Tresca P, Marty M. *Efficacy and tolerance of vinorelbine and fluorouracil combination as first-line chemotherapy of advanced breast cancer: Results of a phase II study using a sequential group method. J Clin Oncol* 1996; 14: 3097-104.
- Zambetti M, Demicheli R, De Candis D, Antonelli G, Giacobone A, Terenziani M, Laffranchi A, Garbagnati F, Biasi S, Bonadonna G. *Five day infusion fluorouracil plus vinorelbine i.v. in metastatic pretreated breast cancer patients. Breast Cancer Res Treat* 1997; 44: 255-60.
- Froudarakis ME, Catimel G, Guastalla JP, Rebatu P, Clavel M. *Phase II trial of navelbine and fluorouracil as second-line chemotherapy in metastatic breast carcinoma. Oncology* 1998; 55: 87-8.
- Cany L, Toulouse C, Ravaud A, Durand M, Mauriac L. *Vinorelbine/5-FU combination in metastatic breast cancer chemotherapy: A retrospective study of 63 cases. Eur J Cancer* 1996; 32A: 370-1.
- Mackean M, Planting A, Twelves C, Schellens J, Allman D, Osterwalder B, Reigner B, Griffin T, Kaye S, Verweij J. *Phase I and pharmacologic study of intermittent twice daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. J Clin Oncol* 1998; 16: 2977-85.
- Budman DR, Meropol NJ, Reigner B, Creaven PJ, Lichtman SM, Berghom E, Behr J, Gordon RJ, Osterwalder B, Griffin T. *Preliminary studies of a novel oral fluoropyrimidine carbamate: Capecitabine. J Clin Oncol* 1998; 16: 1795-802.
- Blum JL, Jones SE, Buzdar AU, LoRusso PM, Kuter I, Vogel C, Osterwalder B, Burger HU, Brown CS, Griffin T. *Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol* 1999; 17: 485-93.
- Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H. *Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. Clin Cancer Res* 1998; 4: 1013-9.
- Endo M, Shinbori N, Fukase Y, Sawada N, Ishikawa T, Ishitsuka H, Tanaka Y. *Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine (Xeloda) or 5'-deoxy-5-fluorouridine (Furtulon) by cyclophosphamide in mammary tumor models. Int J Cancer* 1999; 83: 127-34.
- Ishitsuka H. *Capecitabine: preclinical pharmacology studies. Invest New Drugs* 2000; 18: 343-54.
- Tonkin K, Scarfe AG, Koski S, Bodnar D, Smylie M, Au HJ, Nabholz JM, Mackey JR. *Preliminary Results of a Phase I/II Study of Weekly Docetaxel (Taxotere®) Combined with Intermittent Capecitabine (Xeloda®) for Patients with Anthracycline Pre-Treated Metastatic Breast Cancer. Proc Am Soc Clin Oncol* 2001; 20 (Abstr 2016).
- Maher JF, Villalona-Calero MA. *Taxanes and capecitabine in combination: rationale and clinical results. Clin Breast Cancer* 2002; 2: 287-93.
- Meza LA, Amin B, Horsey M, Petralia SA, Szatrowski TP, Gradishar WJ. *A Phase II Study of Capecitabine in Combination with Paclitaxel as First or Second Line Therapy in Patients with Metastatic Breast Cancer (MBC). Proc Am Soc Clin Oncol* 2001; 20 (Abstr 2029).
- Sawada N, Fujimoto-Ouchi K, Ishikawa T. *Antitumor activity of combination therapy with capecitabine plus vinorelbine, and capecitabine plus gemcitabine in human tumor xenograft models. Proc Am Assoc Cancer Res* 2002; 21 (Abstr 5388).
- Stuart N, Bishop JL, Johnson SRD, Smith IE, O'Brien M, Whipp EC, Gregory K, Laing RW. *Vinorelbine and capecitabine (VX) for advanced breast cancer a phase II study showing good activity and potential for further development. Proc Am Soc Clin Oncol* 2003; 22 (Abstr 183).
- Nole F, Catania C, Mandala M, Munzone E, Rocca A, Zampino G, Minchella I, Noverasco C, Colleoni M, Marrocco E, Lambiase A, Goldhirsch A. *Phase I Study of Vinorelbine (V) and Capecitabine (C) in Advanced Breast Cancer (ABC). Proc Am Soc Clin Oncol* 2000; 19 (Abstr 428).
- Welt A, Borquez D, Oberhoff C, Tewes M, Flmer F, Mohrbacher R, Vanhoefer U, Seeber S. *Phase I study of capecitabine and vinorelbine in pretreated patients with metastatic breast cancer. Proc Am Soc Clin Oncol* 2001; 20 (Abstr 1979).
- Lorusso V, Crucitta E, Silvestris N, Guida M, Misino A, Latorre A, De Lena M. *A phase I study of capecitabine in combination with vinorelbine in advanced breast cancer. Clin Breast Cancer* 2003; 4:

- 138-41.
30. Ahn JH, Kim SB, Ahn SH, Lee JS, Kim WK. *Phase II study of a combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: Final Results. Proc Am Soc Clin Oncol 2003; 22 (Abstr 2030).*
31. NCI common toxicity criteria.<http://ctep.info.nih.gov/CTC3/ctc.htm>.
32. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L, Twelves C, Van Hazel G, Verma S, Leonard R. *Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002; 20: 2812-23.*
33. Jassem J, Pienkowski T, Pluzanska A, Jelic S, Gorbunova V, Mrcic-Krmpotic Z, Berzins J, Nagykalnai T, Wigler N, Renard J, Munier S, Weil C. *Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: Final results of a randomized phase III multicenter trial. J Clin Oncol 2001; 19: 1707-15.*
34. Biganzoli L, Cufer T, Bruning P, Coleman R, Duchateau L, Calvert AH, Gamucci T, Twelves C, Fargeot P, Epelbaum R, Lohrisch C, Piccart MJ. *Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter phase III trial. J Clin Oncol 2002; 15: 3114-21.*