

Capecitabine and Vinorelbine as an All-Oral Chemotherapy in HER2-Negative Locally Advanced and Metastatic Breast Cancer

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Key Words

Capecitabine · Vinorelbine · Combination therapy · Breast cancer, advanced

Summary

Background: The oral formulation of vinorelbine together with capecitabine allows for an all-oral combination chemotherapy which promises to raise quality of life of patients with advanced breast cancer. **Patients and Methods:** Patients with HER2-negative, locally advanced, inoperable or metastatic breast cancer were included in this prospective observational trial (treatment schedule: capecitabine 500 mg/m² twice daily, days 1–14; vinorelbine 60 mg/m², days 1+8; repeated in 3-week cycles). **Results:** All 32 patients (median age 50 years) were evaluable for toxicity, and 30 patients for response. Twenty-four patients received therapy as first-line treatment, and 8 patients as beyond first-line treatment. Median time to progression was 8 months, and median overall survival was 32 months. Complete response was observed in 1 patient (3%), partial response in 10 patients (33%), and disease stabilization for more than 6 months (SD > 6) in 10 patients (33%). This results in an overall response rate (ORR) of 37% and a clinical benefit rate (ORR + SD > 6) of 70%. The only grade 3/4 toxicities were neutropenia (19%) and hand-foot syndrome (9%). **Conclusions:** The all-oral combination of capecitabine/vinorelbine at this schedule appears to be an effective, well-tolerated regimen for treatment of advanced breast cancer, and offers a promising alternative to single-agent capecitabine and vinorelbine as well as intravenous polychemotherapy.

Schlüsselwörter

Capecitabin · Vinorelbin · Kombinationschemotherapie · Mammakarzinom, fortgeschrittenes

Zusammenfassung

Hintergrund: Orales Vinorelbin in Kombination mit Capecitabin eröffnet die Möglichkeit eines rein oralen Therapiekonzepts beim fortgeschrittenen Mammakarzinom. Ein solches Regime ist einfach und bequem durchführbar und könnte die Akzeptanz der Therapie steigern. **Patienten und Methoden:** Patientinnen mit HER2-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs wurden in diese prospektive Beobachtungsstudie eingeschlossen (Behandlungsschema: Capecitabin 500 mg/m² zweimal täglich, d1–14; Vinorelbin 60 mg/m², d1+8, Wiederholung d22). **Ergebnisse:** 32 Patientinnen (medianes Alter 50 Jahre) standen für die Bewertung der Toxizität, 30 für die Evaluation des Ansprechens zur Verfügung. Die mediane Zeit bis zum Fortschreiten der Erkrankung betrug 8 Monate, das mediane Gesamtüberleben 32 Monate. Eine komplette Remission wurde bei 1 Patientin (3%), eine partielle Remission bei 10 Patientinnen (33%) und eine stabile Erkrankung für >6 Monate (SD > 6) bei 10 Patientinnen (33%) beobachtet. Die Ansprechrate (ORR) lag somit bei 37% und die CBR (clinical benefit rate = ORR + SD > 6) bei 70%. Die einzigen Grad-3/4-Toxizitäten waren Neutropenie (19%) und Hand-Fuß-Syndrom (9%). **Schlussfolgerungen:** Die orale Kombinationstherapie bestehend aus Vinorelbin und Capecitabin bietet eine wirksame, gute verträgliche und bequem zu verabreichende Therapieoption für Patientinnen mit fortgeschrittenem Brustkrebs. Sie stellt eine vielversprechende Alternative zur Monotherapie mit den Einzelsubstanzen und zu intravenöser Chemotherapie dar.

Introduction

Breast cancer remains the most frequent cause of cancer death among women [1], and metastatic breast cancer (MBC), while sensitive to chemotherapy, is still incurable. Therefore, quality of life (QoL) issues are of major importance. An oral chemotherapy essentially contributes to QoL by reducing the impact on daily activities: while patients spend a lot of time traveling to, waiting for, and receiving intravenous chemotherapy, oral chemotherapy can be administered at home. In addition, oral cytotoxic drugs are cost-saving [2].

Capecitabine, an oral fluoropyrimidine, shows significant efficacy both as a single agent and in combination, and has emerged as a valuable treatment option in MBC [3–5]. Vinorelbine is a semi-synthetic vinca alkaloid and yields first-line overall response rates (ORR) of 35–59% in MBC [6–8]. Also, the activity of the oral formulation has been assessed in several trials, with time to progression (TTP) in the range of 4–6 months and ORR of 24–31% [9–12]. Preclinical data suggested synergistic activity of capecitabine and vinorelbine [13]. A series of phase II studies investigated the combination of intravenous vinorelbine and capecitabine in chemotherapy-naïve and heavily pretreated MBC, showing promising results (ORR 49–70%) and manageable toxicity [14–16]. Two phase I studies with an all-oral combination of vinorelbine and capecitabine recommended a dosage of capecitabine 2,000 mg/m² and vinorelbine 60 mg/m² [17, 18]. Based upon those data, several phase II studies were initiated [19–23]. Here, we present the results of a prospective observational trial investigating the activity and safety of an all-oral combination chemotherapy of vinorelbine (Navelbine oral[®], Pierre Fabre Pharma, Freiburg, Germany) and capecitabine (Xeloda[®], Roche Pharma AG, Grenzach-Wyhlen, Germany) in HER2-negative, locally advanced, inoperable or metastatic breast cancer.

Patients and Methods

All data were collected at the Department of Medicine I, Clinical Division of Oncology, Medical University of Vienna, Austria. All patients gave written informed consent, and treatment conformed to the ethical regulations of the Medical University of Vienna.

Eligibility

Criteria for inclusion were as follows: histologically confirmed HER2-negative, locally advanced, inoperable or metastatic breast cancer with measurable or immeasurable disease; performance status 0–1 on ECOG (Eastern Cooperative Oncology Group) scale, predicted life expectancy > 3 months; adequate baseline hematological parameters (white blood cell (WBC) count ≥ 3,500/μl, platelet count ≥ 100,000/μl, hemoglobin levels > 9 g/dl) and organ functions (serum bilirubin < 1.5 mg/dl, serum creatinine < 1.5 mg/dl, left ventricular ejection fraction (LVEF) > 55%). Prior adjuvant or palliative treatments with cytotoxic or endocrine drugs were allowed.

Pretreatment Evaluation

Confirmation of metastatic disease was achieved by computed tomography (CT) scans of the chest and abdomen and mammography, with fur-

Table 1. Patient characteristics (n = 32)

ECOG performance score 0–1, n (%)	32 (100)
Age at diagnosis, median (range), years	50 (32–70)
Stage at diagnosis, n (%)	
I	1 (3.1)
II	10 (31.3)
III	12 (37.5)
IV	8 (25.0)
n.a.	1 (3.1)
Grading, n (%)	
1	2 (6.3)
2	14 (43.8)
3	14 (43.8)
n.a.	2 (6.3)
Histology, n (%)	
Ductal	21 (65.6)
Lobular	10 (31.3)
n.a.	1 (3.1)
Hormone receptor status, n (%)	
Estrogen receptor-positive	23 (71.9)
Progesterone receptor-positive	14 (43.8)
HER2 status (IHC/FISH), n (%)	
HER2++ / FISH–	4 (12.5)
HER2+	6 (18.8)
HER2–	22 (68.8)
Prior endocrine therapy, n (%)	
Adjuvant	13 (40.6)
Palliative	16 (50.0)
Prior chemotherapy, n (%)	
Neoadjuvant/adjuvant	19 (59.4)
Palliative	8 (25.0)
Anthracycline	17 (53.1)
Taxane	11 (34.4)
Time to recurrence, median (range), months	59 (15–180)
Treatment line, n (%)	
First-line	24 (75.0)
Second-line	7 (21.9)
Third-line	1 (3.1)
Number of metastatic sites, median (range), n	2 (0–4)
More than one metastatic site, n (%)	19 (59.4)
Metastatic sites, n (%)	
Locally advanced inoperable	1 (3.3)
Visceral (v) only	3 (9.4)
Non-visceral (nv) only	17 (53.1)
Bones only	8 (25.0)
Visceral and non-visceral	11 (34.4)
Location of metastasis, n (%)	
Bones (nv)	23 (71.9)
Soft tissue (nv)	10 (31.3)
Lung (v)	8 (25.0)
Liver (v)	7 (21.9)
Lymph nodes (nv)	6 (18.8)
Local recurrence (nv)	3 (9.4)
Brain (v)	0 (0.0)
Other (v)	3 (9.4)

ECOG = Eastern Cooperative Oncology Group; n.a. = not available;

HER2 = human epidermal growth factor receptor 2;

IHC = immunohistochemistry; FISH = fluorescence in situ hybridization;

v = visceral; nv = non-visceral.

ther work up if indicated. HER2 status was assessed by immunohistochemistry (Herceptest[®], Dako A/S, Glostrup, Denmark) or dual color fluorescence in situ hybridization (FISH; PathVision[®] HER2 DNA probe kit, Vysis Inc., Downers Grove, IL, USA). Tumors were classified as HER2-negative if either the Herceptest was negative/1+ or FISH analysis showed no gene amplification.

Treatment Schedule

Each 3-week cycle consisted of 500 mg/m² capecitabine twice daily (2 weeks on, 1 week off), and 60 mg/m² oral vinorelbine on days 1 and 8. The vinorelbine dose was rounded to a multiple of 10. Treatment was conducted in an outpatient setting. Patients received a diary for daily documentation of medication intake and adverse events. Treatment was continued unless disease progressed or intolerable toxicities occurred. In the case of obvious non-compliance or patient refusal, treatment was discontinued as well.

Follow-Up Evaluation

Complete blood cell count and differential WBC count were performed on days 1, 8, and 15 of the first cycle; if no grade III/IV neutropenia was observed, a single test previous to the following cycle was done. For each cycle, toxicities were graduated according to the Common Terminology Criteria for Adverse Events v3.0 (CTCEA), and the worst episode was

reported. Compliance was evaluated by patient diary and counting of remaining tablets. Dose modifications were performed if toxicities grade II/III occurred: at the first appearance, treatment was delayed for 1 week or until toxicity resolved to grade I or better. In the case of reappearance or grade III toxicity, treatment was interrupted and the dose of either one or both drugs reduced to 75%, ultimately to 50% of the original dose, and maintained during all next cycles. The use of granulocyte colony-stimulating factor (G-CSF) was permitted.

Response Evaluation

According to the UICC guidelines, tumor response was assessed every 3 cycles. Additional staging was performed at any time if clinical symptoms of disease progression emerged. The best achieved overall response for each patient, classified using standard UICC criteria, was reported.

Statistical Analysis

The primary endpoint was TTP. ORR, clinical benefit rate (CBR), tolerability, and overall survival (OS) were defined as secondary endpoints. TTP and OS were estimated by the Kaplan-Meier method. Differences between TTP curves were evaluated using the log-rank test. All statistics were calculated using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient Characteristics

Between March 2004 and June 2008, 32 patients (median age 50 years, range 32–70) with locally advanced, inoperable or metastatic breast cancer were entered as eligible for capecitabine/vinorelbine treatment. All patients received at least 1 cycle of the study medication and were included in the intention-to-treat analysis of toxicity. Of those, 30 patients are evaluable for response. One patient was excluded from the evaluation because of insufficient compliance; the other patient withdrew her consent prior to the first tumor evaluation. Detailed characteristics of all 32 patients are shown in table 1.

Response

Median time of observation was 13 months (range 3–53). Median TTP was 8 months (range 2–35, 95% confidence interval (CI) 7.25–16.12) (fig. 1). The log-rank test revealed no significant differences between the TTP curves for first-line (24 patients) and beyond first-line treatment (6 patients). Median OS was 32 months (range 5–53, 95% CI 24.46–41.55). Efficacy data are summarized in table 2.

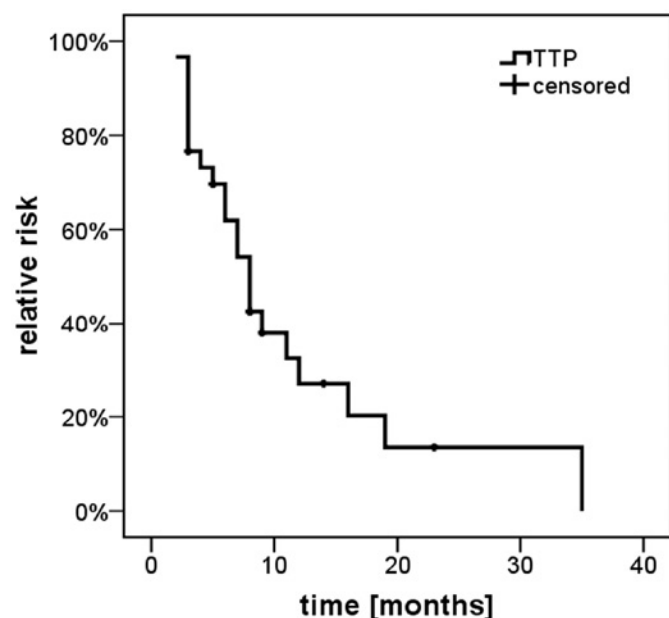


Fig. 1. Time to progression (TTP) in months (n = 30). Events: 22 (73%), censored: 8 (27%), median time: 8.0 months.

Table 2. Response rates (n = 30)

	Response, n (%) ^a						
	CR	PR	ORR	SD ≥ 6	CBR	SD < 6	PD
Overall (n = 30)	1 (3.3)	10 (33.3)	11 (36.7)	10 (33.3)	21 (70.0)	1 (3.3)	8 (26.7)
First-line (n = 24)	1 (4.2)	7 (29.2)	8 (33.3)	8 (33.3)	16 (66.7)	1 (4.2)	7 (29.2)
Beyond first-line (n = 6)	– (–)	3 (50.0)	3 (50.0)	2 (33.3)	5 (83.3)	– (–)	1 (16.7)

^aAccording to UICC criteria.

CR = Complete response; PR = partial response; ORR = overall response rate (CR + PR);

SD ≥ 6 = stable disease lasting at least 6 months; CBR = clinical benefit rate (ORR + SD ≥ 6); SD < 6 = stable disease lasting less than 6 months; PD = progressive disease.

Table 3. Toxicities (n = 32)

Toxicity	Grade, n (%) ^a				
	all	I	II	III	IV
Anemia	22 (68.8)	16 (50.0)	6 (18.8)	– (–)	– (–)
Neutropenia	19 (59.4)	5 (15.6)	8 (25.0)	4 (12.5)	2 (6.3)
Thrombocytopenia	10 (31.3)	10 (31.3)	– (–)	– (–)	– (–)
Nausea	17 (53.1)	8 (25.0)	9 (28.1)	– (–)	– (–)
Vomiting	13 (40.6)	8 (25.0)	5 (15.6)	– (–)	– (–)
Diarrhea	13 (40.6)	12 (37.5)	1 (3.1)	– (–)	– (–)
Fatigue	12 (37.5)	8 (25.0)	4 (12.5)	– (–)	– (–)
Hand-foot syndrome	11 (34.4)	3 (9.4)	5 (15.6)	3 (9.4)	– (–)
Polyneuropathia	4 (12.5)	3 (9.4)	1 (3.1)	– (–)	– (–)
Stomatitis	2 (6.3)	2 (6.3)	– (–)	– (–)	– (–)
Alopecia	2 (6.3)	2 (6.3)	– (–)	– (–)	– (–)

^aAccording to the CTCAE criteria v3.0; the worst episode for each patient was reported.

Toxicity

The total number of cycles administered was 331, with a median of 8 cycles per patient (range 1–47). Toxicities are summarized in table 3. Neutropenia grade IV was observed in 2 patients (6%), while 4 patients (13%) suffered from neutropenia grade III. One patient with neutropenia grade IV developed neutropenic fever and had to be admitted to hospital. Only 3 cases (9%) of grade III hand-foot syndrome were observed. Nausea and vomiting, toxicities important for compliance with an all-oral regimen, were seen frequently (53 and 41%, respectively), yet only 3 patients (9%) discontinued treatment because of nausea grade II. Two patients experienced arterial occlusion (posterior tibial artery and common iliac artery, respectively), and 1 patient a pulmonary embolism while on treatment. In 17 patients (53%), treatment was delayed for at least 1 week. In 5 patients (16%), the dose of both drugs was reduced to 75%, in 6 patients (19%) only the dose of capecitabine was reduced.

Discussion

Considering the putative synergistic effect of vinorelbine and capecitabine, a combination of those agents might result in enhanced anti-tumor activity. This study, while suggesting high clinical activity, is limited by the relatively small number of patients and the fact that 53% presented with non-visceral metastases only. The low median age may be explained by the fact that investigators will often regard healthy patients as ideal candidates for combination chemotherapy. Therefore, our data require confirmation in larger controlled trials.

Regarding efficacy, this regimen appears active with 8 months TTP and 36.7% ORR. For capecitabine as first-line monotherapy, TTP of 3–4.1 months and response rates of 30–36% were reported [4, 24]. Intravenous vinorelbine as first-line treatment yielded 5.8 months TTP and 41% ORR [6]. In pretreated patients, Gasparini et al. [25] reported 4.5 months TTP and 36% ORR. Similar efficacy results were obtained in

a phase II study of oral vinorelbine [11]. Our results, on the other hand, compare well to data of intravenous as well as oral vinorelbine in combination with capecitabine (TTP 7.6–10.5 months) [15, 16, 22, 23, 26], suggesting superior efficacy over the respective single agents.

Side effects were predictable. The relatively low hematological toxicity (only 1 patient developed neutropenic fever) is probably caused by the low dose of vinorelbine. Although hand-foot syndrome and gastrointestinal toxicities were common, influence on compliance was low due to dose reduction (dosage of capecitabine and vinorelbine was reduced in 35 and 16%, respectively). Three cardiovascular incidents (arterial occlusions and pulmonary embolism) occurring during the study period were not thought to be associated with the study drugs; interestingly, Nolè et al. [23] also reported 5 cases of thrombosis. When compared to toxicity profiles of single-agent capecitabine and vinorelbine [27], our regimen showed a far better profile in almost all categories, probably due to lower doses of both drugs. As for the combination of capecitabine and intravenous vinorelbine, results reported by Welt et al. [15] compare well to our data. Two other studies, in contrast, reported a far better toxicity profile [14, 16]. Concerning capecitabine/oral vinorelbine, Nolè et al. [23] reported a higher incidence of neutropenia grade III/IV (47%), diarrhea (67%), and stomatitis (40%), and a similar percentage of hand-foot syndrome (37%). Of note, a third dosage of 60 mg/m² vinorelbine on day 15 was administered, probably causing the higher toxicity and study discontinuation rate (19%). In contrast, Finek et al. [22] demonstrated a very low number of grade III/IV side effects. In sum, side effects were manageable, and this combination appears superior to other combination treatments in terms of toxicity.

Allowing for treatment in an outpatient setting, an all-oral chemotherapy essentially contributes to QoL [2]. Compliance was considered good. Overdosing was not a relevant problem; however, 1 patient had to be excluded from the evaluation because of overdosing vinorelbine, resulting in severe toxicities.

Conclusion

In summary, our results indicate that capecitabine and oral vinorelbine is a reasonably well tolerated and active treatment option in advanced breast cancer. To confirm those results, larger controlled clinical trials are warranted. Fit patients with anthracycline and taxane pretreatment might be candidates for this regimen.

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Conflict of Interest

R. Bartsch has received lecture honoraria from Roche (Xeloda) and Pierre Fabre (Navelbine). M. Gnant has received lecture honoraria and research support from Roche. C.C. Zielinski has received speaker's fees and honoraria for participation in advisory boards from Roche. G.G. Steger has received speaker's fees from Boehringer Ingelheim (Navelbine) and speaker's fees, honoraria for participation in advisory boards, and research support from Roche. All other authors declared no conflict of interest.

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